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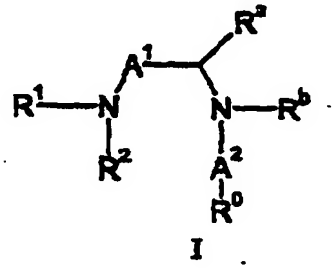
(54) Amine derivatives for the treatment of apoptosis

(57) The present invention is related to substituted amine derivatives I notably for use as pharmaceutically active compounds, as well as to pharmaceutical formulations containing such piperazine derivatives of carbazole. Said substituted amine derivatives are efficient modulators, in particular inhibitors, of the Bax function and/or activation. The present invention is furthermore related to novel substituted amine derivatives as well as methods of their preparation.

A^1 and A^2 are selected independently from each other from the group consisting of -C(O)- and -SO_2-.

R^a, R^b, R^0, R^1 and R^2 are as the application.



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Description

Field of the invention

[0001] The present invention is related to new substituted amine derivatives for use as pharmaceutically active compounds, as well as pharmaceutical formulations containing such substituted amine derivatives useful for the treatment and/or prevention of disorders associated with apoptosis, including neurodegenerative disorders, diseases associated with polyglutamine tracts, epilepsy, ischemia, infertility, cardiovascular disorders, renal hypoxia, hepatitis and AIDS. Said amine derivatives display a modulatory and most notably an inhibitory activity of the cellular death agonist Bax and/or the activation pathways leading to Bax and allows therefore to block the release of cytochrome c. The present invention is furthermore related to novel pharmaceutically active substituted amino derivatives as well as to methods of their preparation.

Background of the invention

[0002] Apoptosis denotes the complex contortions of the membrane and organelles of a cell as it undergoes the process of programmed cell death. During said process, the cell activates an intrinsic suicide program and systematically destroys itself in a controlled manner or by a self-regulated process. The following series of events can be observed:

- The cell surface begins to bleb and expresses pro-phagocytic signals. The whole apoptotic cell then fragments into membrane-bound vesicles that are rapidly and neatly disposed of by phagocytosis, so that there is minimal damage to the surrounding tissue.
- The cell then separates from its neighbors.
- The nucleus also goes through a characteristic pattern of morphological changes as it commits genetic suicide. The chromatin condenses and is specifically cleaved to fragments of DNA.

[0003] Neuronal cell death plays an important role in ensuring that the nervous system develops normally. It appears that the death of developing neurons depends on the size of the target that they innervate : cells with fewer synaptic partners are more likely to die than those that have formed multiple synapses. This may reflect a process, which balances the relative number of pre- to postsynaptic neurons in the developing nervous system. Although neuronal cell death was assumed to be apoptotic, it was only recently that neurons in developing rodent brain were conclusively shown to undergo apoptosis as classified by morphology and DNA fragmentation.

[0004] Neuronal death occurs via either apoptotic or necrotic processes following traumatic nerve injury or during neurodegenerative diseases. Multiple components are emerging as key players having a role in driving neuronal programmed cell death. Amongst the components leading to neuronal apoptosis are protein members belonging to the Bcl-2 family (see Jacobson, M. D. 1997. *Current Biology* 7:R 277-R281; Kroemer, G. C. 1997. *Nature Medicine:* 614-620; Reed, J. C. 1997. *Nature* 387:773-776).

[0005] The entire Bcl-2 family comprises both anti-apoptotic (Bcl-2, Bcl-x_L, Bcl-w, Mcl-1, A1, NR-13, BHRF1, LMW5-HL, ORF16, KS-Bcl-2, E1B-19K, CED-9) and pro-apoptotic (Bax, Bak, Bok, Bik, Blk, Hrk, BNIP3, Bim$_L$, Bad, Bid, EGL-1) molecules (see Kelekar, A., and C. B. Thomp-son 1998. *Trends in Cell Biology* 8:324-330). The specific member thereof, i.e. the first found, Bcl-2 is a 26 kDa protein that localizes to the mitochondrial, endoplasmatic reticulum and perinuclear membranes. The Bcl-2 family proteins can form homo- and hetero-dimers that involve amino acid sequences known as Bcl-2 homology (BH) domains. So far, four of said domains (BH1 to 4) have been identified, the BH3 having been attributed a particularly prominent role in view of the death-promoting cascade. Said BH3 domain of the pro-apoptotic members appears to be required for the interaction between anti and pro-apoptotic molecules. The principal site of action of some of the Bcl-2 family members seems to be the mitochondria. Mitochondria have been shown to play a major role in many types of apoptosis. In particular, this organelle has been shown to release Apoptosis Inducing Factor and cytochrome c, a hemoprotein which is bound to the outer surface of the inner mitochondrial membrane. Said cytochrome c has been shown to trigger caspase 9 activation through Apaf-1/caspase 9 complex formation. Bcl-2 family members play a key role in regulating cytochrome c release. While Bcl-2 and Bcl-x_L have been shown to suppress cytochrome c release, Bax has been found to stimulate this event both in vitro using isolated mitochondria as well as in intact cells following heterologous expression (Martinou et al.; *The Journal of Cell Biology*, 128, 1995, 201-208). The mechanisms by which these proteins perform their function are currently unknown. The three-dimensional structure of Bcl-xL and Bid revealed structural similarities between these proteins and the channel-forming domains of the bacterial toxins colicins and diphtheria toxins. Consistent with such structural similarity, some members of this family including Bax were also found able to form ion channels in synthetic lipid membranes.

[0006] Studies performed with Bax-deficient mice led to the conclusion that Bax plays a prominent role within the

apoptosis pathways, notably in neuronal apoptosis. Bax is viewed to be essential for apoptosis induced by NGF deprivation in neonatal sympathetic neurons or for apoptosis induced in cerebellar granule cells by potassium deprivation from the culture medium. Moreover, it was found that in the Bax-deficient mice (knock-out) neonatal moto-neurons from the facial nucleus can survive following axotomy (see Deckwerth, T.L., Elliott J.L., Knudson C.M. et al. 1996. *Neuron* 17, 401-41). Hence, the inhibition of the Bax activity leading to the prevention of cytochrome c release from mitochondria during apoptosis, is viewed to be useful to protect neurons and also other cell types from various cell death stimuli.

[0007] In WO 97/01635 (Neurex Corp.) the inhibition of apoptosis in an effort to promote cell survival is suggested to be achieved by introducing into the cell a chimeric gene containing a polynucleotide encoding a Bax-ω-polypeptide (a splice variant of the Bax gene, which displays - in contrast to Bax - an anti-apoptotic activity) being operably linked to a promoter effective to cause transcription of the polynucleotide in the cell. It is reported that the expression of the Bax-ω-polypeptide is effective to inhibit apoptosis in the cell.

[0008] Perez et al. in *Nat. Genet. 1999*, 21(2), 200-203 have indicated that apoptosis plays a fundamental role in follicular atresia and they suggest to selectively disrupt the Bax function in order to extend the ovarian lifespan.

[0009] Bax down-regulation up to inhibition could indeed represent an interesting therapy for all diseases associated with apoptosis, including neurodegenerative diseases (e.g. Alzheimer's disease, Parkinson's disease, diseases associated with polyglutamine tracts including Huntington's disease, spino-cerebellar ataxias and dentatorubral-pallidoluysian atrophy; amyotrophic lateral sclerosis, retinitis pigmentosa and multiple sclerosis, epilepsy), ischemia (stroke, myocardial infarction and reperfusion injury), infertility (like premature menopause, ovarian failure or follicular atresia), cardiovascular disorders (arteriosclerosis, heart failure and heart transplantation), renal hypoxia, hepatitis and AIDS.

[0010] Hence, it is an objective of the present invention to provide compounds enabling the treatment of a whole variety of apoptosis-related disorders, including notably the above mentioned diseases.

[0011] It was specifically an objective of the present invention to provide a treatment of apoptosis related disorders by specifically regulating the Bax function, e.g. by modulating, notably by inhibiting, the Bax function or by down-regulating, up to inhibiting, the Bax activation.

[0012] It is notably an objective of the present invention to provide relatively small molecule pharmaceuticals, more specifically non-proteinaceous molecules that avoid essentially all of the drawbacks arising from the use of large bio-peptides or bio-proteins (e.g. restricted bioavailability as well as problems arising from in vivo intolerance thereto), however, which are suitable for the treatment of a number of diseases associated with abnormal apoptosis. It was particularly an objective of the present invention to provide relatively small molecule chemical compounds being suitable Bax modulators (e.g. compounds inhibiting the Bax function or inhibiting the Bax activation) so to be available for a convenient method of treating diseases involving abnormal apoptosis. Moreover, it was an objective of the present invention to provide methods for preparing said small molecule chemical compounds. It was furthermore an objective of the present invention to provide a new category of pharmaceutical formulations for the treatment of a host of diseases. It was finally an objective of the present invention to provide a method of treating diseases that are caused by abnormal apoptosis.

Description of the invention

[0013] The aforementioned objectives have been met according to the independent claims which are set out hereinafter in the description. Preferred embodiments are set out within the dependent claims.

[0014] The following paragraphs provide definitions of the various chemical moieties that make up the compounds according to the invention and are intended to apply uniformly through-out the specification and claims unless an otherwise expressly set out definition provides a broader definition.

[0015] "C_1-C_{18}-alkyl" refers to monovalent alkyl groups having 1 to 18 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-hexyl and the like.

[0016] "Aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 18 carbon atoms having a single ring (e.g. phenyl) or multiple condensed rings (e.g. naphthyl). Preferred aryl include phenyl, naphthyl and the like.

[0017] "Heteroaryl" refers to a monocyclic heteromatic, or a bicyclic or a tricyclic fused-ring heteroaromatic group. Particular examples of heteroaromatic groups include optionally substituted pyridyl, pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,1,3,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, 3H-indolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, quinolizinyl, quinazolinyl, pthalazinyl, quinoxalinyl, cinnnolinyl, napthyridinyl, pyrido[3,4-b] pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolyl, isoquinolyl, tetrazolyl, 5,6,7,8-tetrahydroquinolyl, 5,6,7,8-tetrahydroisoquinolyl, purinyl, pteridinyl, carbazolyl, xanthenyl or benzoquinolyl.

[0018] "Alkenyl" refers to alkenyl groups preferable having from 2 to 18 carbon atoms and having at least 1 or 2 sites of alkenyl unsaturation. Preferable alkenyl groups include ethenyl (-CH=CH_2), n-propenyl (-CH_2CH=CH_2) and the like.

[0019] "Alkynyl" refers to alkynyl groups preferably having 2 to 18 carbon atoms and having at least 1-2 sites of alkynyl unsaturation, preferred alkynyl groups include ethynyl (-C≡CH), propargyl (-CH_2C≡CH), and the like.

[0020] "Alkoxy" refers to the group "C_1-C_6-alkyl-O-" or "-O-aryl" or "O-heteroaryl". Preferred alkoxy groups include by way of example, methoxy, ethoxy, phenoxy and the like.

[0021] "Halogen" refers to fluoro, chloro, bromo and iodo atoms.

[0022] "Sulfonyl" refers to group "R-SO_2" wherein R is selected from aryl, heteroaryl, C_1-C_{18}-alkyl, C_1-C_{18}-alkyl substituted with halogen atoms e.g. a CF_3-SO_2 group.

[0023] "Sulfoxy" refers to a group "R-S(=O)-" wherein R is selected from C_1-C_6-alkyl, C_1-C_6-alkyl substituted with halogen atoms e.g. a CF_3-SO- group, aryl, heteroaryl.

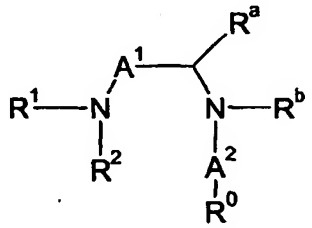
[0024] "Thioalkoxy" refers to groups "C_1-C_6-alkyl-S-", "aryl-S-", "heteroaryl-S-". Preferred thioalkoxy groups include thiomethoxy, thioethoxy, and the like.

[0025] "Substituted or unsubstituted" : Unless otherwise constrained by the definition of the individual substituent, the above set out groups, like alkyl, heteroaryl, alkenyl, alkynyl and aryl etc. groups can optionally be substituted with from 1 to 5 substituents selected from group consisting of C_1-C_{18}-alkyl, acetoxy, alkoxy, alkenyl, alkynyl, primary, secondary or tertiary amino groups or quarternary ammonium moieties, aminocarbonyl, alkoxycarbonyl, aryl, carboxyl, cyano, halogen, hydroxy, nitro, sulfoxy, sulfonyl, thioalkoxy, trihalomethyl and the like. Alternatively said substitution could also comprise situations where neighbouring substituents have undergone ring closure, notably when viccinal functional substituents are involved, thus forming e.g. lactams, lactons, cyclic anhydrides, but also acetals, thioacetals, aminals formed by ring closure for instance in an effort to obtain a protective group.

[0026] "Pharmaceutically acceptable salts or complexes" refers to salts or complexes that retain the desired biological activity of the below-identified compounds of formula I. Examples of such salts include, but are not restricted to acid addition salts formed with inorganic acids (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like), and salts formed with organic acids such as trifluoroacetic acid, acetic acid, oxalic acid, tartaric acid, succinic acid, malic acid, fumaric acid, maleic acid, ascorbic acid, benzoic acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene sulfonic acid, naphthalene disulfonic acid, and polygalacturonic acid. Said compounds can also be administered as pharmaceu-tically acceptable quaternary salts known by a person skilled in the art, which specifically include the quaternary ammonium salt of the formula —NR,R',R" + Z^-, wherein R, R', R" is independently hydrogen, alkyl, or substituted benzyl, and Z is a counterion, including chlo-ride, bromide, iodide, -O-alkyl, toluenesulfonate, methylsulfonate, sulfonate, phosphate, or carboxylate (such as benzoate, succinate, acetate, glycolate, maleate, malate, fumarate, citrate, tartrate, ascorbate, cinnamoate, mandeloate, trifluoroacetate and diphenylacetate).

[0027] "Pharmaceutically active derivative" refers to any compound that upon administration to the recipient, is capable of providing directly or indirectly, the compounds disclosed herein. "Enantiomeric excess" (ee) refers to the products that are obtained by an essentially enantiomeric synthesis or a synthesis comprising an enantioselective step, whereby a surplus of one enantiomer in the order of at least about 52% ee is yielded. In the absence of an enantiomeric synthesis, racemic products are usually obtained that do however also have the inventive set out activity as modulators of the Bax function, e.g. Bax inhibitors (antagonists).

[0028] Quite surprisingly, it was now found that compounds according to formula I are suitable pharmaceutically active agents, notably by effectively modulating the Bax function or the Bax activation.



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[0029] A^1 and A^2 are selected independently from each other from the group consisting of-C(O)- and -SO_2-.

[0030] R^a is C_1-C_{10} alkyl, R^b is CH_3, or R^a and R^b taken together with the atoms to which they are attached form a five-membered saturated ring optionally containing a sulfur atom or a six-membered saturated ring optionally fused with an aryl or heteroaryl group.

[0031] R^1 is either H or C_1-C_6 alkyl.

[0032] R^2 is -$(R^d$-$X_1)_m$-R^e wherein m is an integer from 0 to 8.

[0033] Therein, R^d is selected of aryl, heteroaryl, C_1-C_{18} alkyl, 3-8-membered cycloalkyl, C_2-C_{18} alkenyl or 3-8-mem-

bered cycloalkenyl, C_2-C_{18} alkynyl.

[0034] X_1 is a bond, O, NH, NR^g, $NR^gN^{g'}$, S, $Si(R^gR^{g'})$, SO, SO_2, wherein R^g and $R^{g'}$ are independently selected from the group consisting of substituted or unsubstituted C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl or heteroaryl.

[0035] R^e is selected of aryl- C_1-C_{18} alkyl, aryl- C_2-C_{18} alkenyl, aryl- C_2-C_{18} alkynyl, heteroaryl-C_1-C_{18} alkyl, heteroaryl- C_2-C_{18} alkenyl, heteroaryl- C_2-C_{18} alkynyl, C_1-C_{18} alkyl, C_2-C_{18} alkenyl, C_2-C_{18} alkynyl, said C_1-C_{18} alkyl, C_2-C_{18} alkenyl and C_2-C_{18} alkynyl have a polar terminal substituent of the formula -NRR' or —N^+RR'R" wherein R, R', R" are selected independently from each other of H, C_1-C_6-alkyl, preferably methyl or ethyl. Alternatively, at least 2 of R, R' and R" form a 3-12 membered cyclic or bicyclic ring. A terminal ammonium moiety of the formula —N^+RR'R", with all groups R, R' and R" being organic residues represents one preferred embodiment. A further preferred terminal amino group is —NH_2.

[0036] Also R^1 and R^2 together with the N atom to which they are attached could form an unsubstituted or substituted 4-12 membered unsaturated or saturated ring containing one further heteroatom selected from O, N. Such a ring containing a further heteroatom provides for the polar moiety which is crucial for the compounds of formula (I). In order to further increase or modify the polarity such a ring arising from ring closure of R^1 and R^2 said ring may optionally be substituted by R^e, whereby R^e is as defined above.

[0037] Also, R^1 and R^2 together with the N atom to which they are attached could form an unsubstituted or substituted 4-12 membered unsaturated or saturated ring which is substituted by R^e, or directly by a polar terminal substituent of the formula -NRR' or —N^+RR'R" wherein R, R', R" are H, C_1-C_6-alkyl.

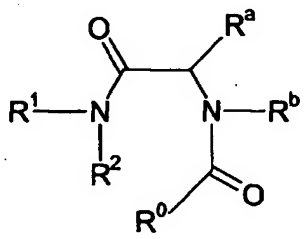
[0038] R^0 is R^f-X_2-$R^{f'}$ wherein

[0039] R^f and $R^{f'}$ are independently from each other selected from the group consisting of aryl, heteroaryl, 3-8-membered cycloalkenyl, 3-8-membered cycloalkyl, C_2-C_{18} alkyl, C_2-C_{18} alkenyl, C_2-C_{18} alkynyl, aryl- C_1-C_{18} alkyl, aryl- C_2-C_{18} alkenyl, aryl- C_2-C_{18} alkynyl, heteroaryl- C_1-C_{18} alkyl, heteroaryl- C_2-C_{18} alkenyl, heteroaryl- C_2-C_{18} alkynyl,

[0040] X_2 is a bond or O, S, $Si(R^gR^{g'})$, SO, SO_2, wherein R^g and $R^{g'}$ are selected as above defined.

[0041] The present invention also includes the pharmaceutically acceptable salts, e.g. hydrates, acid addition salts thereof, as well as the pharmaceutically active derivatives of compounds of formula I. Preferred pharmaceutically acceptable salts of the compound I, are acid addition salts formed with pharmaceutically acceptable acids like hydrochloride, hydrobromide, trifluoroacetate, sulfate or bisulfate, phosphate or hydrogen phosphate, acetate, benzoate, succinate, fumarate, maleate, lactate, citrate, tartrate, gluconate, methanesulfonate, benzenesulfonate, and *para*-toluenesulfonate salts.

[0042] According to a preferred embodiment of the invention, A^1 and A^2 are each carbonyl (C=O) thus providing preferred compounds as illustrated by the below formula IA:



IA

wherein R^0, R^1, R^2, R^a and R^b are as above-defined.

[0043] It was unexpectedly found that the above set out compounds according to formula I are suitable modulators of the Bax function. They preferably mimick the Bax protein's surface in such a way that a binding thereto is possible. For the purpose of the preferred binding of the modulators to the Bax protein, it turns out to be important that R^0 represents a globally unpolar chain, preferably a long lipophilic alkyl or aryl group, optionally containing one or more heteroatoms, but no functional groups imparting a polar character to said moiety R^0.

[0044] Particularly preferred R^0 is a C_8-C_{18} alkyl group more preferred R^0 is a C_{10}-C_{18} alkyl group and most preferred is a C_{12}-alkyl group.

[0045] At the same time - still for the purposes of the preferred binding of said compounds according to formula I to the Bax protein - R^2 must have a polar character or end which could ideally be or involve an amino, or an alcohol function. According to one preferred embodiment, R^2 comprises a long alkyl chain, preferably with R^e being a C_{10}-C_{18} alkyl having a terminal amino group NRR' or OR, particularly preferred is a C_{10}-C_{18} alkyl having a terminal NH_2 group or OH group. Also, a terminal quartemary ammonium moiety of the formula -N^+RR'R" of R^2 wherein each R, R', R"

are a C_1-C_6-alkyl or which form a cyclic or bicyclic ring, imparts the necessary polarity to the molecules of formula I.

[0046] According to a further preferred embodiment, R^a and R^b form either

- a five-membered saturated ring, optionally containing a sulfur atom, or
- a six-membered saturated ring wherein said ring may be fused with an unsubstituted phenyl group.

[0047] Preferred rings following to ring closure of R^a and R^b are pyrrolidinyl, piperidinyl, a fused piperidinyl, e.g. a tetrahydroisoquinolinyl (TIC) or 1,3-thiazolidinyl.

[0048] Particularly preferred amine derivatives are those wherein R^1 is H or CH_3, most preferred H, R^2 is $-(R^d-X_1)_m-R^e$ in which R^d-X_1 is $-(CH_2)_2-O-$ or a bond, R^e is C_1-C_{10}-alkylamine, most preferred R^2 is C_2-C_8 alkylamine. Specific examples for R^2 is ethylenamine, hexylenamin or heptylenamine.

[0049] Particularly preferred amine derivatives are those wherein R^0 is selected from the group consisting of unsubstituted C_4-C_{18} alkyl having optionally a terminal cyclohexyl group. Particularly preferred R^0 is C_8-C_{18} alkyl, more preferred C_{10}-C_{18} alkyl and most preferred C_{12} alkyl. Further specific examples of R^0 are $-CH_2$-phenyl-O-CH_2-phenyl or $-CH_2$-Ph-Ph.

[0050] Where R^a and R^b form a five-membered saturated ring, optionally containing a sulfur atom, or a six-membered saturated ring optionally, optionally fused with an unsubstituted phenyl group, preferably A^1 and A^2 are each (C=O), R^0 is an unsubstituted C_4-C_{16} alkyl having optionally a terminal cyclohexyl group or $-CH_2$-Ph-O-CH_2-Ph or CH_2-Ph-Ph, R^1 is H or-CH_3, R^2 is $(R^d-X_1)_m-R^e$ wherein R^d-X_1 is $-(CH_2)_2-O-$ with m being 0 or 2, R^e is an unsubstituted C_2-C_8-alkylamine, more preferred a C_2-C_7 alkylamine and most preferred a hexylenamine.

[0051] A particularly preferred embodiment is wherein R^a and R^b form a piperidinyl, pyrrolidinyl or thiazolidinyl ring optionally fused with an unsubstituted phenyl group, A^1 and A^2 are each C=O, R^0 is an unsubstituted C_4 or C_{12} alkyl chain, R^1 is H or CH_3, R^2 is $-(R^d-X_1)_m-R^e$ wherein m is 0 and R^e is C_2-C_8 alkylamine.

[0052] Where R^a and R^b do not form any ring, a preferred embodiment of the amine derivative according to the present invention is wherein R^b is CH_3, R^a is iPr, A^1 and A^2 are each C=O, R^0 is C_4-C_{15} alkyl, preferably a dodecyl group, R^1 is H, R^2 is $-(R^d-X_1)_m-R^e$ wherein m is 0, R^e is C_4-C_{10}, particularly C_6 alkylamine.

[0053] The compounds of formula I may contain one or more asymmetric centers and may therefore exist as enantiomers or diasteroisomers. It is to be understood that the invention includes both mixtures and separate individual isomers or enantiomers of the compounds of formula I. In a particularly preferred embodiment the pyrrolidine derivatives according to formula I are obtained in an enantiomeric excess of at least 52 % ee, preferably of at least 92-98% ee.

[0054] Specific examples of compounds of formula I include the following:

(S)-N-(6-Aminohexyl)-1-tridecanoylpiperidine-2-carboxamide

(R)-N-(6-Aminohexyl)-1-tridecanoylpiperidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}piperidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-(4-cyclohexylbutanoyl)piperidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-([1,1'-biphenyl]-4-ylacetyl)piperidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)piperidine-2-carboxamide

(S)-N-(6-Aminohexyl)-1-tridecanoylpyrrolidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}pyrrolidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-(4-cyclohexylbutanoyl)pyrrolidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-([1,1'-biphenyl]-4-ylacetyl)pyrrolidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carboxamide

(±)-N-(6-Aminohexyl)-3-tridecanoyl-1,3-thiazolidine-4-carboxamide

(±)-N-(6-Aminohexyl)-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide

(±)-N-(6-Aminohexyl)-3 -(4-cyclohexylbutanoyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(6-Aminohexyl)-3-([1,1'-biphenyl]-4-ylacetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(6-Aminohexyl)-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(6-Aminohexyl)-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(6-Aminohexyl)-2-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(6-Aminohexyl)-2-(4-cyclohexylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3 -carbox-amide

(+)-N-(6-Aminohexyl)-2-([1,1'-biphenyl] -4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(6-Aminohexyl)-2-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,2,3,4 tetrahydroisoquinoline-3-carboxamide

(S)-N-(1-{ [(6-Aminohexyl)amino] carbonyl}-2-methylpropyl)-N-methyltridecanamide

(±)-N-(6-Aminohexyl)-11-methyl-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide

(±)-N-(6-Aminohexyl)-2-[(4-cyclohexylbutanoyl)(methyl)amino]-3-methylbutanamide

(±)-N-(6-Aminohexyl)-2-[([1,1'-biphenyl]-4-ylacetyl)(methyl)amino]-3-methylbutanamide

(±)-N-(6-Aminohexyl)-3-methyl-2-[methyl({4-[(phenylmethyl)oxy]phenyl}acetyl)amino]butanamide

(±)-N-(5-Aminopentyl)-1-tridecanoylpiperidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}piperidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-(4-cyclohexylbutanoyl)piperidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-([1,1'-biphenyl]-4-ylacetyl)piperidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)piperidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-tridecanoylpyrrolidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}pyrrolidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-(4-cyclohexylbutanoyl)pyrrolidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-([1,1'-biphenyl]-4-ylacetyl)pyrrolidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carboxamide

(±)-N-(5-Aminopentyl)-3-tridecanoyl-1,3-thiazolidine-4-carboxamide

(±)-N-(5-Aminopentyl)-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide

(±)-N-(5-Aminopentyl)-3-(4-cyclohexylbutanoyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(5-Aminopentyl)-3-([1,1'-biphenyl]-4-ylacetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(5-Aminopentyl)-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(5-Aminopentyl)-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(5-Aminopentyl)-2-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-((5-Aminopentyl)-2-(4-cyclohexylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(5-Aminopentyl)-2-([1,1'-biphenyl]-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(5-Aminopentyl)-2-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(1-{[(5-Aminopentyl)amino]carbonyl}-2-methylpropyl)-N-methyltridecanamide

(±)-N-(5-Aminopentyl)-11-methyl-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide

(±)-N-(5-Aminopentyl)-2-[(4-cyclohexylbutanoyl)(methyl)amino]-3-methylbutanamide

(±)-N-(5-Aminopentyl)-2-[([1,1'-biphenyl]-4-ylacetyl)(methyl)amino]-3-methylbutanamide

(±)-N-(5-Aminopentyl)-3-methyl-2- [methyl({4-[(phenylmethyl)oxy]phenyl}acetyl)amino]butanamide

(±)-N-(7-Aminoheptyl)-1-tridecanoylpiperidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}piperidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-(4-cyclohexylbutanoyl)piperidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-([1,1'-biphenyl]-4-ylacetyl)piperidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-({4-[(phenylmethyl)oxy]phenyl} acetyl)piperidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-tridecanoylpyrrolidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}pyrrolidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-(4-cyclohexylbutanoyl)pyrrolidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-([1,1'-biphenyl]-4-ylacetyl)pyrrolidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-3-tridecanoyl-1,3-thiazolidine-4-carboxamide

(±)-N-(7-Aminoheptyl)-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide

(±)-N-(7-Aminoheptyl)-3-(4-cyclohexylbutanoyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(7-Aminoheptyl)-3-([1,1'-biphenyl]-4-ylacetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(7-Aminoheptyl)-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(7-Aminoheptyl)-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(7-Aminoheptyl)-2-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(7-Aminoheptyl)-2-(4-cyclohexylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(7-Aminoheptyl)-2-([1,1'-biphenyl]-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(7-Aminoheptyl)-2-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(1-{[(7-Aminoheptyl)amino]carbonyl}-2-methylpropyl)-N-methyltridecanamide

(±)-N-(7-Aminoheptyl)-11-methyl-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide

(±)-N-(7-Aminoheptyl)-2-[(4-cyclohexylbutanoyl)(methyl)amino]-3-methylbutanamide

(±)-N-(7-Aminoheptyl)-2-[([1,1'-biphenyl]-4-ylacetyl)(methyl)amino]-3-methylbutanamide

(±)-N-(7-Aminoheptyl)-3-methyl-2-[methyl({4-[(phenylmethyl)oxy]phenyl}acetyl)amino]butanamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-tridecanoylpiperidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}piperidine-2-carboxamide

(+)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-(4-cyclohexylbutanoyl)piperidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-([1,1'-biphenyl]-4-ylacetyl)piperidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)piperidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-tridecanoylpyrrolidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}pyrrolidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-(4-cyclohexylbutanoyl)pyrrolidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-([1,1'-biphenyl]-4-ylacetyl)pyrrolidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-3-tridecanoyl-1,3-thiazolidine-4-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-3-(4-cyclohexylbutanoyl)-1,3-thiazolidine-4-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-3-([1,1'-biphenyl]-4-ylacetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3 -carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-2-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-2-(4-cyclohexylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3 -carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-2-([1,1'-biphenyl]-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-2-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-[1-({[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl] amino}carbonyl)-2-methylpropyl]-N-methyltridecanamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-11-methyl-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-2-[(4-cyclohexylbutanoyl)(methyl)amino]-3-methylbutanamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-2-[([1,1'-biphenyl]-4-ylacetyl)(methyl)amino] -3 -methylbutanamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-3-methyl-2-[methyl({4-[(phenylmethyl)oxy]phenyl}acetyl)amino] butanamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy} ethyl)oxy]acetyl}piperidine-2-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1-tridecanoylpyrrolidine-2-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy} ethyl)oxy]acetyl}pyrrolidine-2-carboxamide

(±)-1-(4-Cyclohexylbutanoyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)pyrrolidine-2-carboxamide

(±)-1-([1,1'-Biphenyl]-4-ylacetyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)pyrrolidine-2-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1-({4-[(phenylmethyl)oxy]phenyl} acetyl)pyrrolidine-2-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-3-tridecanoyl-1,3-thiazolidine-4-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide

(±)-3-(4-Cyclohexylbutanoyl)-N-methyl-N-(2-{[2-(methylamino)ethyl] oxy} ethyl)-1,3-thiazolidine-4-carboxamide

(±)-3-([1,1'-Biphenyl]-4-ylacetyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1,3-thiazolidine-4-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-2-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-2-(4-Cyclohexylbutanoyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-2-([1,1'-Biphenyl]-4-ylacetyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-2-({4-[(phenylmethyl)oxy]phenyl} acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N,11-Dimethyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}piperidine-2-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-1-tridecanoylpyrrolidine-2-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl} pyrrolidine-2-carboxamide

(±)-1-(4-Cyclohexylbutanoyl)-N-methyl-N- [6-(methylamino)hexyl]pyrrolidine-2-carboxamide

(±)-1-([1,1'-Biphenyl]-4-ylacetyl)-N-methyl-N-[6-(methylamino)hexyl]pyrrolidine-2-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-3-tridecanoyl-1,3-thiazolidine-4-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide

(±)-3-(4-Cyclohexylbutanoyl)-N-methyl-N-[6-(methylamino)hexyl]-1,3-thiazolidine-4-carboxamide

(±)-3-([1,1'-Biphenyl]-4-ylacetyl)-N-methyl-N-[6-(methylamino)hexyl]-1,3-thiazolidine-4-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-2-{[(2-{[2-(methyloxy)ethyl] oxy} ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-2-(4-Cyclohexylbutanoyl)-N-methyl-N-[6-(methylamino)hexyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-2-([1,1'-Biphenyl]-4-ylacetyl)-N-methyl-N-[6-(methylamino)hexyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-2-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N,11-Dimethyl-N-[6-(methylamino)hexyl]-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide

(±)-N-(6-Aminohexyl)-1-pentanoylpiperidine-2-carboxamide

(±)-N-(2-Aminoethyl)-1-pentanoylpiperidine-2-carboxamide

(±)-N-(2-Aminoethyl)-1-tridecanoylpiperidine-2-carboxamide

[0055] Thereby, the most preferred compounds are those which are selected from the group consisting of:

(S)-N-(6-Aminohexyl)-1-tridecanoylpiperidine-2-carboxamide

(R)-N-(6-Aminohexyl)-1-tridecanoylpiperidine-2-carboxamide

(S)-N-(6-Aminohexyl)-1-tridecanoylpyrrolidine-2-carboxamide

(S)-N-(1-{[(6-Aminohexyl)amino]carbonyl}-2-methylpropyl)-N-methyltridecanamide

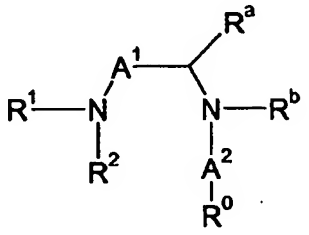
[0056] A further aspect of the present invention consists in the use of compounds according to formula I for the preparation of pharmaceutical compositions and their use for the modulation of the Bax function, or the modulation (e. g. inhibition) of the activation of Bax, respectively, thus providing a convenient method of treatment of Bax-mediated disorders, in particular neuronal disorders and/or disorders of the immune system as well as said pharmaceutical compositions themselves. Said modulation could notably involve the inhibition of the activity (activation) and/or of the expression of Bax. Also, said modulation of the Bax activity could actually comprise the down-regulation, up to the inhibition or disruption, for instance of the Bid interaction with Bax, which has been shown to play a role within the context of the Bax activation leading to cytochrome c release (see Martinou et al. in *The Journal of Cell Biology*, Vol. 144, No. 5, March 8, 1999, pages 891-901). As a result of the inhibition of the Bax activation by Bid upon using the compounds according to formula I, the cytochrome c release could be down-regulated, notably be inhibited or essentially blocked, thus providing a convenient means to modulate the above described apoptosis pathways. As a result, through said modulation of the apoptosis pathways a whole variety of disorders associated with abnor-mal apoptosis could be treated.

[0057] As pointed out above, the compounds of formula I are suitable to be used as a medicament, i.e. they are suitable for use in treating diseases mediated by the Bax function, like disorders of the autoimmune system and the neuronal system of mammals, notably of human beings. More specifically, the compounds according to formula I, alone or in the form of a pharmaceutical composition, are useful for the modulation, in particular for the down-regulation, up to the inhibition, of the Bax function and/or the Bax activation. More specifically, the compounds according to formula I are, alone or in the form of a pharmaceutical composition, useful for the treatment or prevention of disorders associated with abnormal expression or activation of Bax. The compounds according to formula I could be employed alone or in combination with further pharmaceutical agents. The compounds of formula I are suitable to be used as a medicament alone or in the form of a pharmaceutical composition together with suitable carriers, diluents or excipients. The compounds of formula I are suitable to be used for the preparation of orally administrated pharmaceutical compositions.

[0058] Thus, according to the present invention, compounds pursuant to formula I are particularly useful for the treatment or prevention of immuno- and/or neuronal-related diseases or pathological states in which the modulation in particular the inhibition of the Bax function and/or the Bax activation plays a crucial role, such as neurodegenerative diseases (e.g. Alzheimer's disease, Parkinson's disease, diseases associated with polyglutamine tracts including Huntington disease, spinocerebellar ataxias and dentatorubral-pallidoluysian atrophy; amyotrophic lateral sclerosis, Crohn's disease, retinitis pigmentosa and multiple sclerosis, epilepsy), ischemia (stroke, myocardial infarction and reperfusion injury), infertility (like premature menopause, ovarian failure or follicular atresia), cardiovascular disorders (arteriosclerosis, heart failure and heart transplantation), renal hypoxia, hepatitis and AIDS.

[0059] As a matter of fact, prior to the herein reported, surprisingly found pharmaceutically active amino derivatives according to formula I, nothing was known in respect of the use of small molecule chemical compounds as active inhibitors of the pro-apoptosis agent Bax. Nothing was known in respect of the possibility to down-regulate, to disrupt or to substantially block through small molecules the activation of Bax, for instance via Bid (being another Bcl-2 family member which is involved in the pathways leading to the release of cytochrome c).

[0060] A further aspect of the present invention consists in the use of amino derivatives according to formula I for the preparation of a pharmaceutical composition for the treatment or prevention of disorders associated with abnormal Bax function or Bax activation, an abnormal expression or activity of Bax as well as said pharmaceutical compositions themselves. Such a composition could be prepared by using the compounds according to formula I. Hence, such compounds of formula I useful for the preparation of a pharma-ceutical composition for the treatment or prevention of disorders associated with the modulation of the Bax function or activation, in particular with the abnormal expression or activity of Bax have the general formula:



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and its geometrical isomers, in an optically active form as enantiomers, diastereomers, as well as in the form of race-

mate, as well as pharmaceutically acceptable salts thereof, wherein

[0061] A^1 and A^2 are selected independently from each other from the group consisting of -C(O)- and -SO_2-.

[0062] R^a is C_1-C_{10} alkyl, R^b is CH_3, or R^a and R^b taken together with the atoms to which they are attached form a five-membered saturated ring optionally containing a sulfur atom or a six-membered saturated ring optionally fused with an aryl or heteroaryl group.

[0063] R^1 is either H or C_1-C_6 alkyl.

[0064] R^2 is -$(R^d$-$X_1)_m$-R^e wherein m is an integer from 0 to 8.

[0065] Therein, R^d is selected of aryl, heteroaryl, C_1-C_{18} alkyl, 3-8-membered cycloalkyl, C_2-C_{18} alkenyl or 3-8-membered cycloalkenyl, C_2-C_{18} alkynyl.

[0066] X_1 is a bond, O, NH, NR^g, $NR^gN^{g'}$, S, $Si(R^gR^{g'})$, SO, SO_2, wherein R^g and $R^{g'}$ are independently selected from the group consisting of substituted or unsubstituted C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl or heteroaryl.

[0067] R^e is selected of aryl- C_1-C_{18} alkyl, aryl- C_2-C_{18} alkenyl, aryl- C_2-C_{18} alkynyl, heteroaryl-C_1-C_{18} alkyl, heteroaryl- C_2-C_{18} alkenyl, heteroaryl- C_2-C_{18} alkynyl, C_1-C_{18} alkyl, C_2-C_{18} alkenyl, C_2-C_{18} alkynyl, said C_1-C_{18} alkyl, C_2-C_{18} alkenyl and C_2-C_{18} alkynyl have a polar terminal substituent of the formula -OR, -NRR' or -N^+RR'R" wherein R, R', R" are selected independently from each other of H, C_1-C_6-alkyl, preferably methyl or ethyl. Alternatively, at least 2 of R, R' and R" form a 3-12 membered cyclic or bicyclic ring. A terminal ammonium moiety of the formula -N^+RR'R", with all groups R, R' and R" being organic residues represents one preferred embodiment. A further preferred terminal amino group is —NH_2 and OH.

[0068] Also R^1 and R^2 together with the N atom to which they are attached could form an unsubstituted or substituted 4-12 membered unsaturated or saturated ring containing one further heteroatom selected from O, N. Such a ring containing a further heteroatom provides for the polar moiety which is crucial for the compounds of formula (I). In order to further increase or modify the polarity such a ring arising from ring closure of R^1 and R^2 said ring may optionally be substituted by R^e, whereby R^e is as defined above.

[0069] Also, R^1 and R^2 together with the N atom to which they are attached could form an unsubstituted or substituted 4-12 membered unsaturated or saturated ring which is substituted by R^e, or directly by a polar terminal substituent of the formula OR, -NRR' or -N^+RR'R" wherein R, R', R" are H, C_1-C_6-alkyl.

[0070] R^0 of the above formula (1) is R^f-X_2-R^f wherein

[0071] R^f and R^f are independently from each other selected from the group consisting of aryl, heteroaryl, 3-8-membered cycloalkenyl, 3-8-membered cycloalkyl, C_2-C_{18} alkyl, C_2-C_{18} alkenyl, C_2-C_{18} alkynyl, aryl- C_1-C_{18} alkyl, aryl- C_2-C_{18} alkenyl, aryl- C_2-C_{18} alkynyl, heteroaryl- C_1-C_{18} alkyl, heteroaryl- C_2-C_{18} alkenyl, heteroaryl- C_2-C_{18} alkynyl,

[0072] X_2 is a bond or O, S, $Si(R^gR^{g'})$, SO, SO_2, wherein R^g and $R^{g'}$ are selected as above defined.

[0073] Still a further object of the present invention is a process for preparing the novel compounds according to formula I which have been set out above.

[0074] Compounds of formula I of this invention can be prepared from readily available starting materials using the following general methods and procedures.

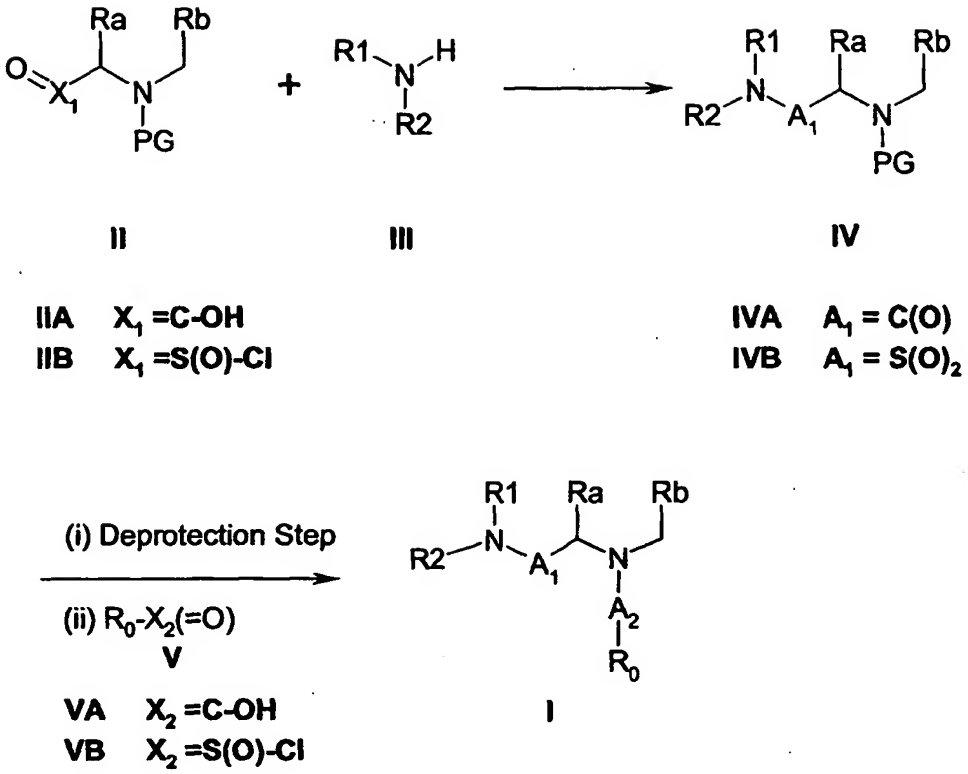
[0075] It will be appreciated that where typical or preferred experimental conditions (i.e. reaction temperatures, time, moles of reagents, solvents, etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by a person skilled in the art by routine optimisation procedures.

[0076] Compounds according to the general formula I could be obtained by two major processes (A) and (B).

[0077] According to the process (A), compounds according to the general formula I are prepared from the corresponding protected amino derivatives as described in the litterature and as set out in the examples ensuing and shown in Scheme I, below.

[0078] Scheme I, wherein A^1 = A^2 are carbonyl (C=O), illustrates the reaction of a protected amino acid derivative of formula IIA with an amino derivative of formula III to form protected amino derivatives of formula IVA. The formula IVA compounds, after a deprotection step, then react with carboxylic acid derivatives of formula VA to form compounds of formula I.

Scheme I



[0079] Scheme I, wherein $A^1 = A^2$ are $S(O)_2$, illustrates the reaction of a protected amino derivative of formula IIB with an amino derivative of formula III to form protected amino derivatives of formula IVB. The formula IVB compounds, after a deprotection step (which is well known by a person skilled in the art), then react with sulfonyl chloride derivatives of formula VB to form compounds of formula I.

[0080] Furthermore, Scheme I, wherein $A^1 = (C=O)$ and $A^2 = S(O)_2$ illustrates the reaction of a protected amino acid derivative of formula IIA with an amino derivative of formula III to form protected amino derivatives of formula IVA. The formula IVA compounds, after a deprotection step, then react with sulfonyl chloride derivatives of formula VB to form compounds of formula I.

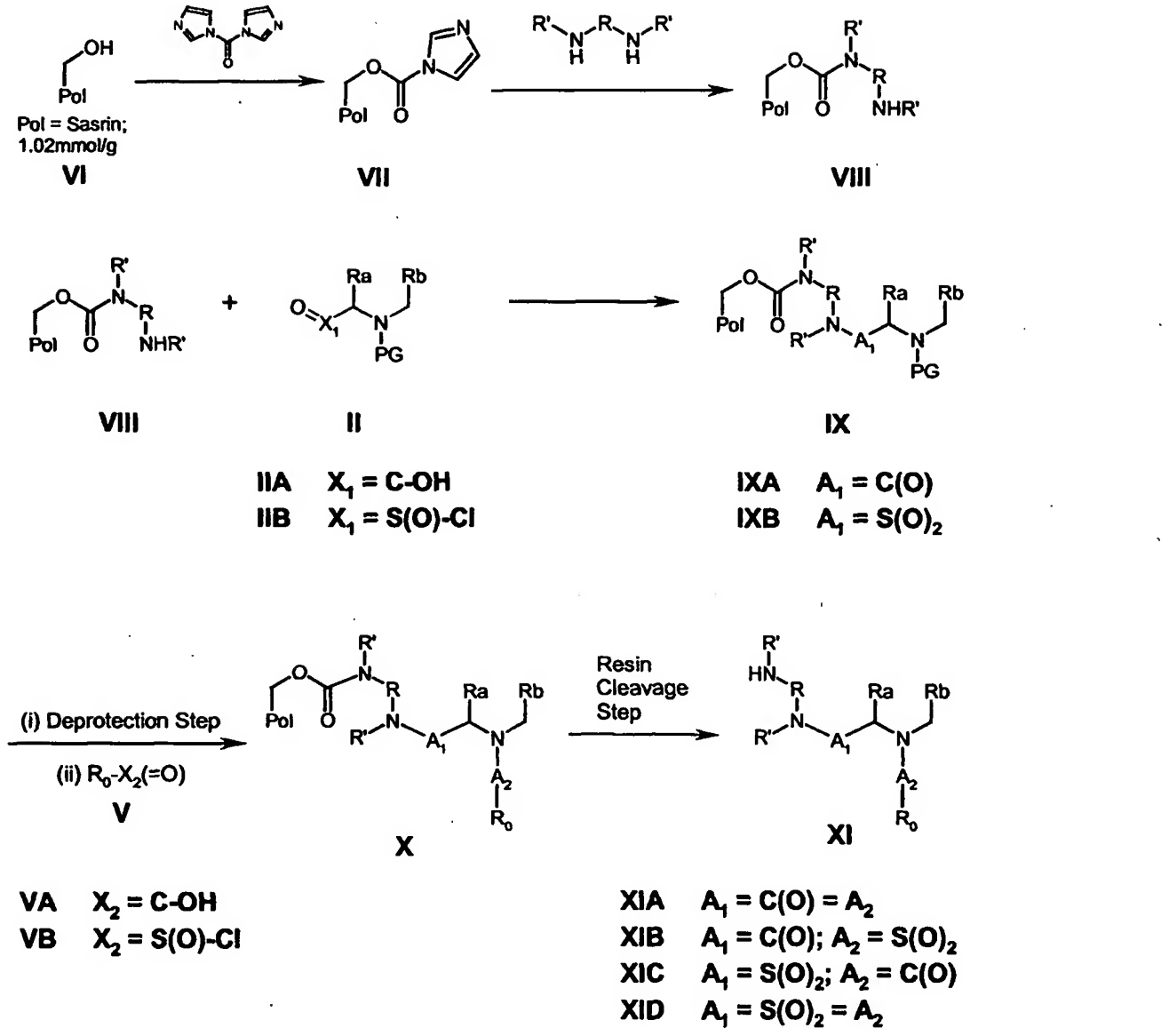
[0081] Furthermore, Scheme I, wherein $A^1 = S(O)_2$ and $A^2 = C(O)$ illustrates the reaction of a protected amino derivative of formula IIB with an amino derivative of formula III to form protected amino derivatives of formula IVB. The formula IVB compounds, after a deprotection step, then react with acid derivatives of formula VA to form compounds of formula I.

[0082] Compounds of formula I can be prepared as individual enantiomers or in an enantiomeric enriched form from the appropriate enantiomer of formula II or as a racemic mixture from the appropriate racemic compound of formula II. Individual enantiomers of the invention can be prepared from racemates by resolution using methods known in the art for the separation of racemic mixtures into their constituent enantiomers, for example using HPLC on a chiral column, or using separation of salts of diastereomers.

[0083] Compounds of formula II, III and V are commercially available compounds or prepared by standard synthetic techniques as hereinafter described in the Examples.

[0084] According to the process (B), compounds according to the general formula I are prepared from the corresponding protected amino derivatives by solid-phase protocols such as described in the examples 2, Table 1 and shown in schemes II and III, below.

Scheme II



[0085] In the solid-phase strategy depicted in Scheme II, symmetrical primary or secondary diamines are attached to acid-labile hydroxymethyl resins VI, such as Sasrin or ArgoGel MB-OH, in the form of a carbamate VIII, which is derived from VI through standard processes well known to the practitioner skilled in the art, e.g. using phosgene equivalents, such as CDI, triphosgene, or others. The free amino group of the carbamate VIII can then be coupled to commercial and non-commercial *N*-protected amino carboxylic acid derivatives IIA using standard peptide coupling protocols well known to the person skilled in the art. After *N*-deprotection, the free amino group can be reacted either with acid derivatives of formula VA, or with sulfonyl chlorides of formula VB, to yield, after acid-catalyzed cleavage from the solid support, compounds of formula XIA, or of formula XIB, respectively.

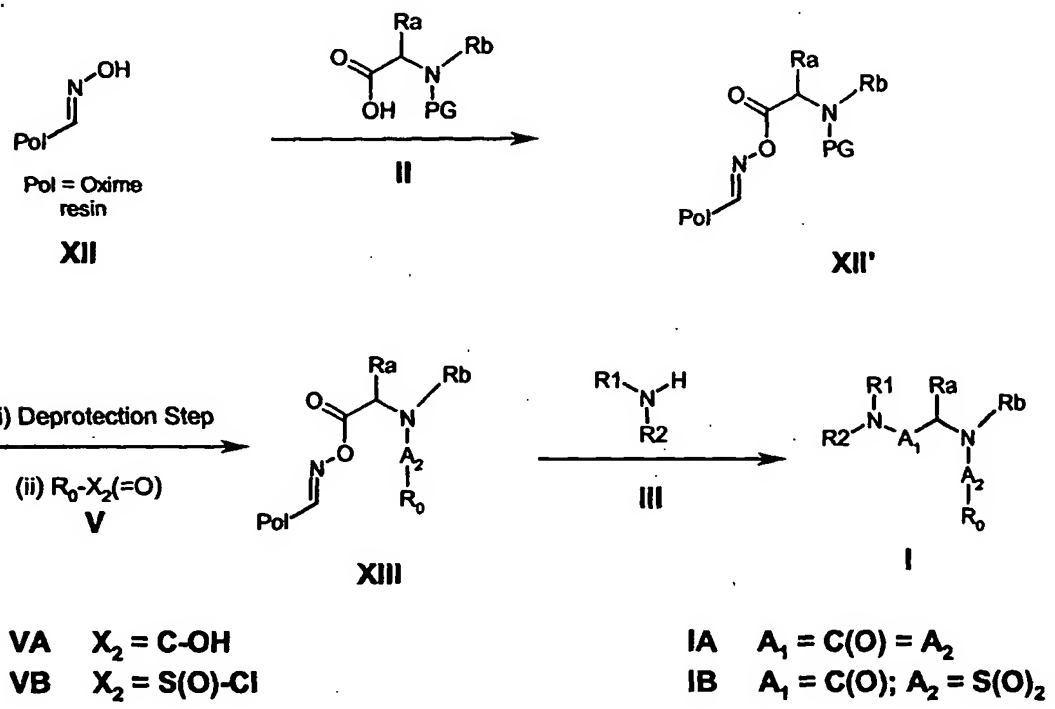
[0086] Alternatively, the free amino group of the carbamate VIII can be reacted with *N*-protected amino derivatives of formula IIB using standard protocols for sulfonamide formation well known to the person skilled in the art. After *N*-deprotection, the free amino group can be reacted either with acid derivatives of formula VA, or with sulfonyl chlorides of formula VB, to yield, after acid-catalyzed cleavage from the solid support, compounds of formula XIC, or of formula

XID, respectively.

[0087] Other derivatives of formula I are prepared using known modifications to the scheme II reaction sequence. Compounds of formula I wherein A is a sulfonyl functionality are prepared by replacing formula II and V with sulfonyl chloride functional groups to yield sulfonamide derivatives.

[0088] Based on a further solid-supported reaction sequence, compounds of formula I can be obtained as illustrated in Scheme III.

Scheme III



VA X_2 = C-OH
VB X_2 = S(O)-Cl

IA $A_1 = C(O) = A_2$
IB $A_1 = C(O)$; $A_2 = S(O)_2$

[0089] According to the general procedures well known to the practitioner in the field of solid-phase synthesis, *N*-protected commercial or non-commercial amino acids II are coupled to oxime resin XII yielding XII'. After *N*-deprotection, the free amino group can be reacted either with acid derivatives of formula VA, or with sulfonyl chlorides of formula VB, to yield, after cleavage from the solid support with primary or secondary amines III, compounds of formula IA, or of formula IB, respectively.

[0090] According to a further general process, compounds of formula I can be converted to alternative compounds of formula I, employing suitable interconversion techniques such as hereinafter described in the Examples.

[0091] Compounds of this invention can be isolated in association with solvent molecules by crystallization from evaporation of an appropriate solvent. The pharmaceutically acceptable acid addition salts of the compounds of formula I, which contain a basic center, may be prepared in a conventional manner. For example, a solution of the free base may be treated with a suitable acid, either neat or in a suitable solution, and the resulting salt isolated either by filtration or by evaporation under vacuum of the reaction solvent. Pharmaceutically acceptable base addition salts may be obtained in an analogous manner by treating a solution of compound of formula I with a suitable base. Both types of salt may be formed or interconverted using ion-exchange resin techniques.

[0092] A final aspect of the present invention is related to the formulations containing the active compounds according to formula I. When employed as pharmaceuticals, the compounds of formula I of the present invention are typically administered in the form of a pharmaceutical composition. Hence, pharmaceutical compositions comprising a compound of formula I and a pharmaceutically acceptable carrier, diluent or excipient therefore are also within the scope of the present invention. A person skilled in the art is aware of a whole variety of such carrier, diluent or excipient compounds suitable to formulate a pharmaceutical composition. Also, the present invention provides compounds for use as a medicament. In particular, the invention provides compounds according to formula I for use as Bax modulators,

i.e. for the treatment of disorders or disease states in mammals, notably in human beings. Said disorders are associated with inappropriate cell death, including neurodegenerative disorders, diseases associated with polyglutamine tracts, epilepsy, ischemia, infertility, cardiovascular disorders, renal hypoxia, hepatitis and AIDS, either alone or in combination with other medicaments.

[0093] The compounds of the invention, together with a conventionally employed adjuvant, carrier, diluent or excipient may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral administration (including subcutaneous use). Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

[0094] When employed as pharmaceuticals, the amino derivatives of this invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of this invention are administered in a pharmaceu-tically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0095] The pharmaceutical compositions of these inventions can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, the compounds are preferably formulated as either injectable or oral compositions. The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampoules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the amino derivative is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

[0096] Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatine; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0097] Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As above mentioned, the compounds of formula I in such compositions is/are typically a minor component, frequently ranging between 0.05 to 10% by weight with the remainder being the injectable carrier and the like.

[0098] The above described components for orally administered or injectable compositions are merely representative. Further materials as well as processing techniques and the like are set out in Part 8 of *Remington's Pharmaceutical Sciences*, 17th Edition, 1985, Marck Publishing Company, Easton, Pennsylvania, which is incorporated herein be reference.

[0099] The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can also be found in the incorporated materials in *Remington's Pharmaceutical Sciences*.

[0100] In the following the present invention shall be illustrated by means of some examples which are not to be construed as limiting the scope of the invention.

Examples

[0101] The following abbreviations are hereinafter used in the accompanying examples: min (minute), hr (hour), g (gram), mmol (millimole), m.p. (melting point), eq (equivalents), mL (milliliter), µL (microliters), mL (milliliters), DCM (dichloromethane), TFA (trifluoroacetic acid), rt (room temperature), DMSO (dimethylsulfoxide), DMSO-d_6 (deuterated dimethylsulfoxide), THF (tetrahydrofuran), Na_2SO_4 (sodium sulfate), $MgSO_4$ (magnesium sulfate), $CDCl_3$ (deuterated chloroform), DIEA, (diisopropylethyl amine), TEA (triethyl amine), EtOAc (ethyl acetate), cHex (cyclohexanes), Et_2O

(diethyl ether), ACN (acetonitrile), $NaHCO_3$ (sodium bicarbonate), HOBt (1-hydroxybenzotriazole), EDCI (1-(3-dimethyl-amino-propyl)-3-ethylcarbodiimide), dimethylformamide (DMF), K_2CO_3 (potassium carbonate), HATU (N-{(dimethylamino)(1H-1,2,3-triazolo[4,5-b]pyridin-1-yl)methylene}-N-methylmethanaminium hexafluorophosphate N-oxide), CDI (carbonyldiimidazole).

Example 1

(S)-1-Tridecanoyl-piperidine-2-carboxylic acid (6-amino-hexyl)-amide

[0102] A solution of (S)-(6-{[1-(1-tridecanoyl-piperidin-2-yl)-methanoyl]-amino}-hexyl)carbamic acid *tert*-butyl ester (3.9 g, 7.45 mmol) in DCM (40 mL) was treated with TFA (8 mL) at - 20 °C for two days until disappearance of the starting material. The reaction mixture was allowed to warm up to rt and was washed with an aqueous saturated solution of K_2CO_3. Extraction, drying over $MgSO_4$ and evaporation *in vacuo* gave a yellow oil. Purification via flash chromatography (SiO_2, 5 x 13 cm^2 column) using a mixture (90:10:2) of DCM:MeOH(5%aqueous solution of NH_3) gave the title compound (1.35 g) as a pale yellow oil. The residue was taken in anhydrous DCM (25 mL) and treated with TFA (246 µL, 365 mg) at - 10 °C. Evaporation of the solvents gave the title compound (1.67 g, 3.11 mmol) as a yellow oil in a 42% yield.
Analysis for $C_{25}H_{49}N_3O_2$. 2TFA.0.037CH_2Cl_2:
Calculated: C, 59.66; H, 9.44; N,7.83 ;
Found: C, 60.04; H, 9.33; N,7.77 %.
[0103] (S)-(6-{[1-(1-Tridecanoyl-piperidin-2-yl)-methanoyl]-amino}-hexyl)-carbamic acid *tert*-butyl ester was obtained by treating a solution of {6-[(1-piperidin-2-yl-methanoyl)amino]hexyl}-carbamic acid tert-butyl ester in DCM (100 mL) with tridecanoic acid (2.36 g, 1.1 equiv.) in the presence of HATU (5.0 g, 1.3 equiv.) and DIEA (4.2 mL, 2.4 equiv.). After 2 hours of stirring at rt the reaction was judged to be complete by tlc monitoring. DCM was added (50 mL) and the reaction mixture was washed 3 times with citric acid (0.5 M). 3 times with an aqueous saturated solution of $NaHCO_3$ and with brine. Drying over Na_2SO_4, evaporation *in vacuo* gave a residue which was purified via flash chromatography (SiO_2) using EtOAc:chexanes (6:4) as eluant. (S)-(6-{[1-(1-Tridecanoyl-piperidin-2-yl)methanoyl]-amino}-hexyl)-carbamic acid *tert*-butyl ester (4.6 g) was obtained as a yellow oil in a 87% yield.
^{1}H-RMN ($CDCl_3/CD_3OD$ (14/1), 300 MHz) δ 5.05 (d, 0.8H), 4.50 (d, 0.2H), 4.37 (d, 0.2H), 3.68 (d, 0.8H), 3.27-2.86 (m, 5H), 2.55-2.05 (m, 3H), 1.70-1.10 (m, 42H), 0.79 (t, 3H).
[0104] {6-[(1-Piperidin-2-yl-methanoyl)-amino]hexyl}-carbamic acid tert-butyl ester was obtained by treating (L)-2-(6-tert-butoxycarbonylamino-hexylcarbamoyl)-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (7.0 g, 12.8 mmol) with 500 mL of a solution piperidine in DMF (20%) for 50 min. After evaporation of the solvent *in vacuo*, the resulting pale yellow solid was flash chromatographed using DCM:MeOH (90:10) as eluant. After evaporation of the solvent *in vacuo* {6-[(1-piperidin-2-yl-methanoyl)-amino]hexyl}carbamic acid tert-butyl ester was obtained a white solid in a 80% yield.
MS (APCI): (M+1) = 328.
To a solution of(L)-piperidine-1,2-dicarboxylic acid 1-(9H-fluoren-9-ylmethyl)ester (5.0 g, 14.2 mmol) in 400 mL of DCM were added (6-amino-hexyl)-carbamic acid tert-butyl ester (3.96 g, 1.1 equiv.), HATU (7.0 g, 1.3 equiv.) and DIEA (10.8 mL, 4.4 equiv.) under inert atmosphere. After 2 hours of stirring at rt the reaction mixture was washed twice with an aqueous solution of HCl (1M), twice with an aqueous saturated solution of $NaHCO_3$ and with brine. After drying over Na_2SO_4, evaporation *in vacuo*, an oily residue was obtained and filtered through a silica plug using a mixture of EtOAc:chexanes (8:2) as eluant. After evaporation *in vacuo* (L)-2-(6-tert-butoxycarbonylamino-hexylcarbamoyl)-piperidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester was obtained as a white foam in a 90% yield. MS (APCI): (M+Na) = 572.

Example 2

(R)-1-Tridecanoyl-piperidine-2-carboxylic acid (6-amino-hexyl)-amide

[0105] To a 500 mg-batch of ArgoGel MB-OH (loading 0.4 mmol/g, 0.2 mmol) was added a solution of 163 mg (1 mmol, 5 eq.) carbonyldiimidazole and 171 µl (1 mmol, 5 eq.) DIEA in 5 ml of dry THF, and the resulting mixture was allowed to react for 7 h at room temperature under gentle shaking. After this time, the resin was washed with THF (2x), DCM (2x), DMF (1x) and then directly used for the following step. The resin was allowed to react for 15h at room temperature with a solution of 230 µl (2 mmol, 10 eq.) 1,6-hexanediamine and 342 µl (2 mmol, 10 eq.) DIEA in 5ml DMF. After this time, the resin batches were washed with DMF (3x), DCM (1x), THF (2x), DCM (3x), and Et_2O (2x) and dried *in vacuo*. To the resulting resin batch was added a solution of 211 mg (0.6 mmol, 3 eq.) Fmoc-D-pipecolic acid, 228 mg (0.6 mmol, 3 eq.) HATU, and 206 µl (1.2 mmol, 6 eq.) DIEA in 3 ml anhydr. DMF. After a reaction time of 8 h

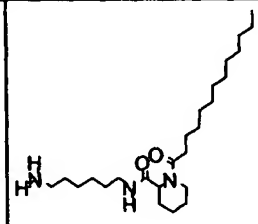
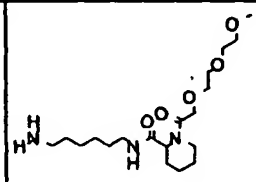
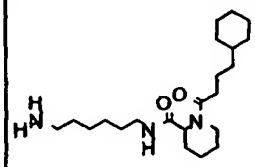
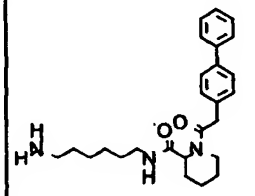
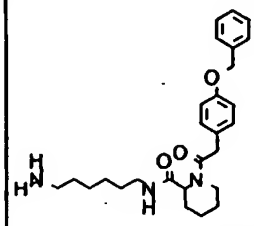
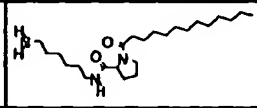
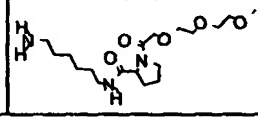
at ambient temperature, the resin was washed with DMF (5x), DCM (5x), DMF (5x), DCM (3x), Et_2O (2x), and dried *in vacuo*. The resin was now treated with 4ml of a solution of 20% (v/v) piperidine in DMF for 20min at room temperature, then washed with DMF (5x), DCM (5x), DMF (5x). To the resulting resin was added a solution of 129 mg (0.6 mmol, 3 eq.) tridecanoic acid, 228 mg (0.6 mmol, 3 eq.) HATU, and 206 µl (1.2 mmol, 6 eq.) DIEA in 3 ml anhydr. DMF. After a reaction time of 8h at room temperature, the reaction was worked up by washing with DMF (5x), DCM (5x), DMF (5x), DCM (3x), Et_2O (2x), and the resin batches were dried *in vacuo* at r.t. O/N. The resin was treated with a solution of 20% (v/v) TFA in DCM for 10 min at room temperature, to release the title compound from the resin in 60% overall yield.

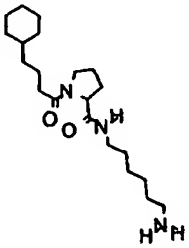
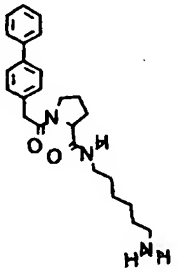
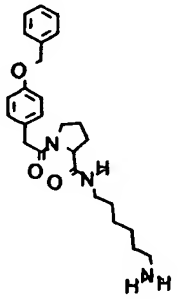
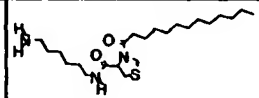
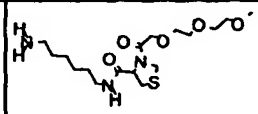
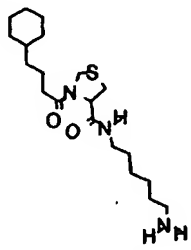
^{1}H-RMN ($CDCl_3$, 300 MHz) δ 8.14 (bs, 3H), 6.74 (bs, 1H), 5.06 (bs, 0.85H), 4.53 (d, 0.15H), 4.44 (bs, 0.15H), 3.73 (d, 0.85H), 3.23 (m, 3H), 2.99 (bs, 2H), 2.34 (bs, 2H), 2.14 (d, 1H), 1.85-1.15 (m, 33H), 0.86 (t, 3H).

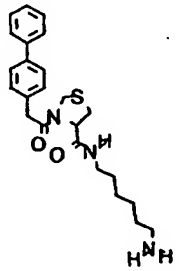
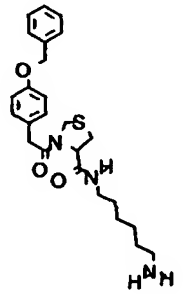
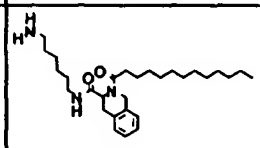
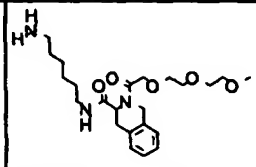
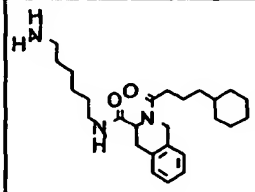
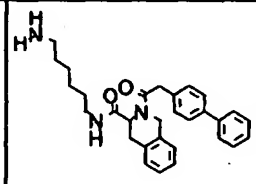
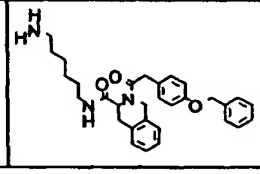
Examples 3 through 138

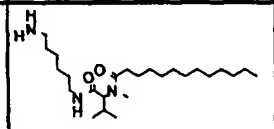
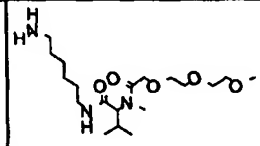
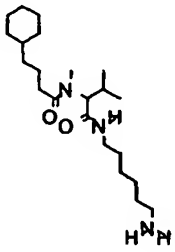
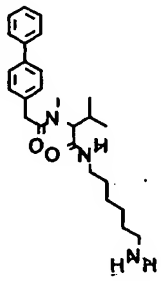
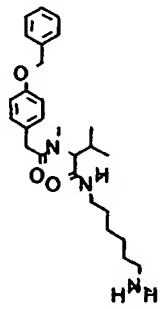
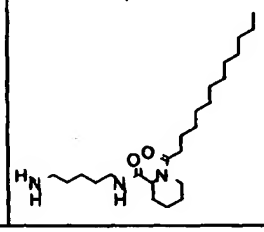
[0106] The compounds belonging to examples 3 through 138 were prepared according to the procedure outlined above for example 2, by using the corresponding set out starting materials, with overall yields ranging from 50-90%, and in high purities (see Table 1).

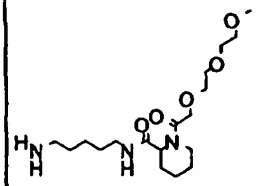
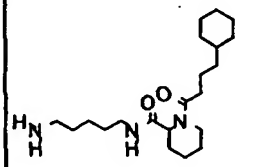
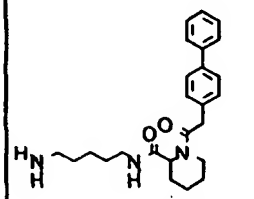
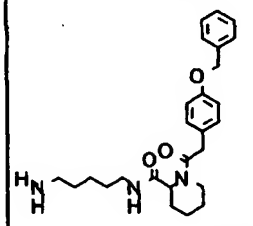
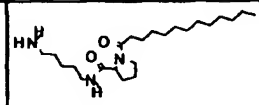
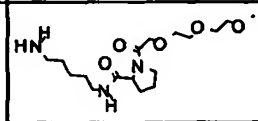
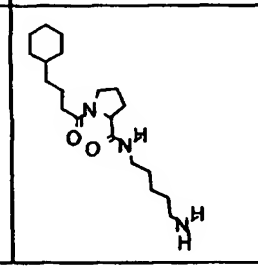
Table 1 (Examples 2 – 138):

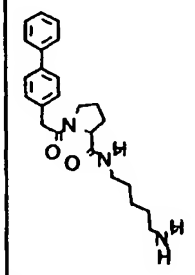
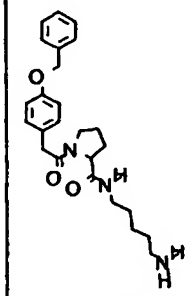
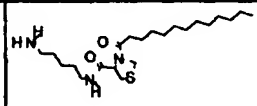
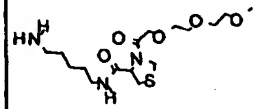
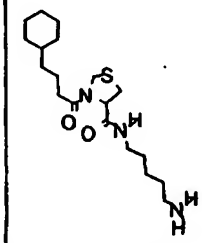
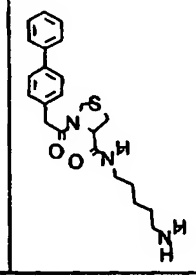
Ex. No.	Structure	IUPAC Name	MW	Purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
2		(R)-N-(6-aminohexyl)-1-tridecanoylpiperidine-2-carboxamide	423.69	n/a	424.2	422.4
3		N-(6-aminohexyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl} piperidine-2-carboxamide	387.52	n/a	388.2	386.0
4		N-(6-aminohexyl)-1-(4-cyclohexylbutanoyl)piperidine-2-carboxamide	379.59	n/a	380.2	379.0
5		N-(6-aminohexyl)-1-([1,1'-biphenyl]-4-ylacetyl)piperidine-2-carboxamide	421.59	82%	422.2	420.0
6		N-(6-aminohexyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl) piperidine-2-carboxamide	451.61	76%	452.2	450.2
7		(S)-N-(6-aminohexyl)-1-tridecanoylpyrrolidine-2-carboxamide	409.66	n/a	410.2	408.2
8		N-(6-aminohexyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl} pyrrolidine-2-carboxamide	373.50	n/a	374.0	372.0

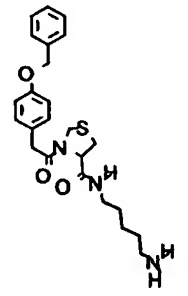
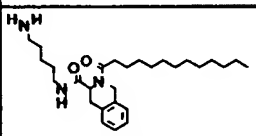
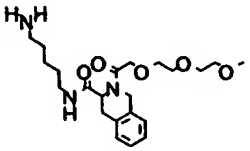
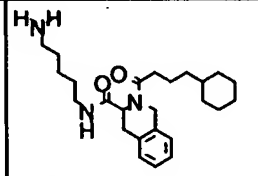
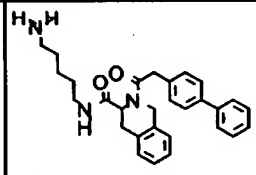
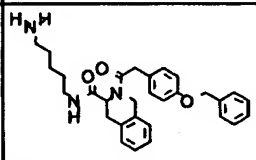
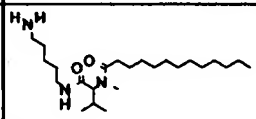
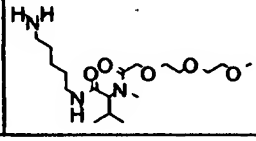
Ex. No.	Structure	IUPAC Name	MW	Purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
9		N-(6-aminohexyl)-1-(4-cyclohexylbutanoyl)pyrrolidine-2-carboxamide	365.56	n/a	366.2	364.3
10		N-(6-aminohexyl)-1-([1,1'-biphenyl]-4-ylacetyl)pyrrolidine-2-carboxamide	407.56	96%	408.0	406.0
11		N-(6-aminohexyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carboxamide	437.59	96%	438.2	436.0
12		N-(6-aminohexyl)-3-tridecanoyl-1,3-thiazolidine-4-carboxamide	427.70	n/a	428.2	426.2
13		N-(6-aminohexyl)-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide	391.53	n/a	392.2	390.2
14		N-(6-aminohexyl)-3-(4-cyclohexylbutanoyl)-1,3-thiazolidine-4-carboxamide	383.60	n/a	384.2	382.0

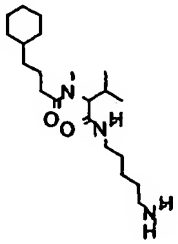
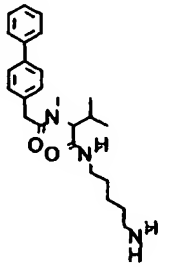
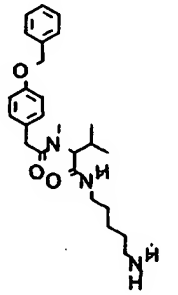
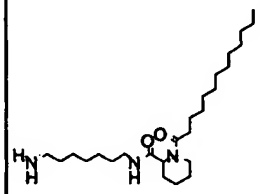
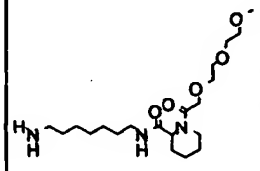
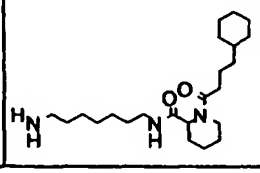
Ex. No.	Structure	IUPAC Name	MW	Purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
15		N-(6-aminohexyl)-3-([1,1'-biphenyl]-4-ylacetyl)-1,3-thiazolidine-4-carboxamide	425.60	90%	426.2	424.0
16		N-(6-aminohexyl)-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide	455.62	94%	456.2	454.0
17		N-(6-aminohexyl)-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	471.73	97%	472.4	470.2
18		N-(6-aminohexyl)-2-[[(2-[[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	435.57	96%	436.2	434.2
19		N-(6-aminohexyl)-2-(4-cyclohexylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	427.64	94%	428.2	426.0
20		N-(6-aminohexyl)-2-([1,1'-biphenyl]-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	469.63	93%	470.2	468.2
21		N-(6-aminohexyl)-2-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	499.66	95%	500.2	498.2

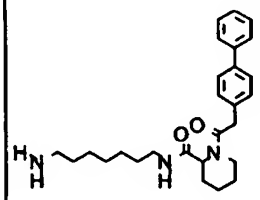
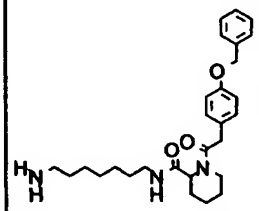
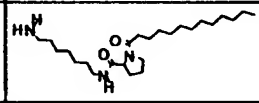
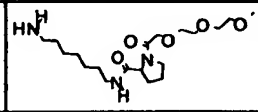
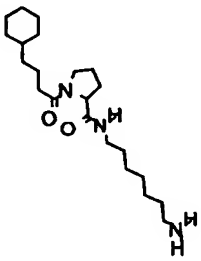
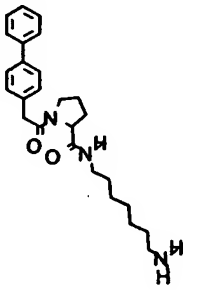
Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
22		(S)-N-(1-{[(6-aminohexyl)amino]carbonyl}-2-methylpropyl)-N-methyltridecanamide	425.70	n/a	426.4	424.4
23		N-(6-aminohexyl)-11-methyl-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide	389.54	n/a	390.2	388.0
24		N-(6-aminohexyl)-2-[(4-cyclohexylbutanoyl)(methyl)amino]-3-methylbutanamide	381.61	n/a	382.2	380.2
25		N-(6-aminohexyl)-2-[([1,1'-biphenyl]-4-ylacetyl)(methyl)amino]-3-methylbutanamide	423.60	85%	424.2	422.4
26		N-(6-aminohexyl)-3-methyl-2-[methyl({4-[(phenylmethyl)oxy]phenyl}acetyl) amino]butanamide	453.63	83%	454.2	452.2
27		N-(5-aminopentyl)-1-tridecanoylpiperidine-2-carboxamide	409.66	n/a	410.2	408.2

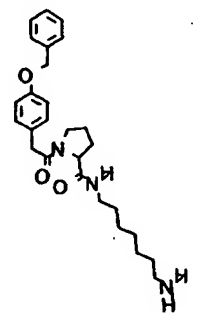
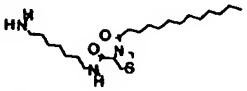
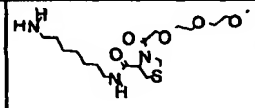
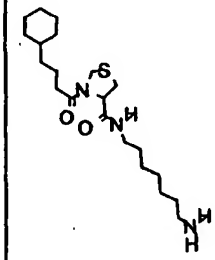
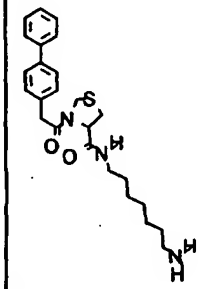
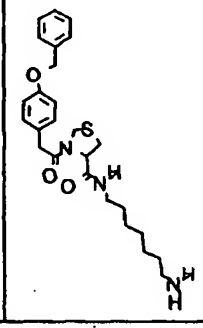
Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
28		N-(5-aminopentyl)-1-[[(2-[[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl) piperidine-2-carboxamide	373.50	n/a	374.0	372.2
29		N-(5-aminopentyl)-1-(4-cyclohexylbutanoyl)piperidine-2-carboxamide	365.56	n/a	366.2	364.2
30		N-(5-aminopentyl)-1-([1,1'-biphenyl]-4-ylacetyl)piperidine-2-carboxamide	407.56	84%	408.2	406.2
31		N-(5-aminopentyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)piperidine-2-carboxamide	437.59	82%	438.2	436.0
32		N-(5-aminopentyl)-1-tridecanoylpyrrolidine-2-carboxamide	395.63	n/a	396.2	394.2
33		N-(5-aminopentyl)-1-[[(2-[[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl) pyrrolidine-2-carboxamide	359.47	n/a	360.2	358.0
34		N-(5-aminopentyl)-1-(4-cyclohexylbutanoyl)pyrrolidine-2-carboxamide	351.54	n/a	352.0	350.0

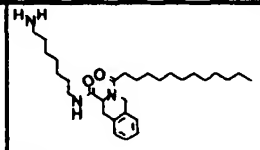
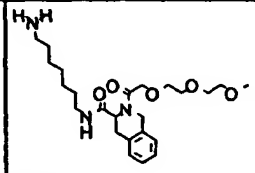
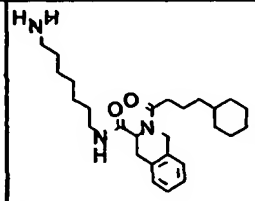
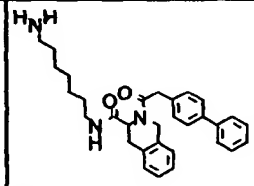
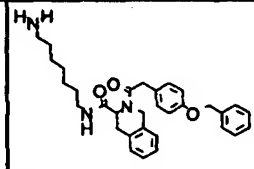
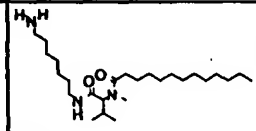
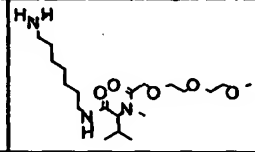
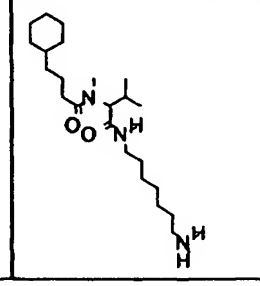
Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
35		N-(5-aminopentyl)-1-([1,1'-biphenyl]-4-ylacetyl)pyrrolidine-2-carboxamide	393.53	97%	394.2	392.0
36		N-(5-aminopentyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carboxamide	423.56	97%	424.2	422.2
37		N-(5-aminopentyl)-3-tridecanoyl-1,3-thiazolidine-4-carboxamide	413.67	n/a	414.2	412.0
38		N-(5-aminopentyl)-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide	377.51	n/a	378.0	376.0
39		N-(5-aminopentyl)-3-(4-cyclohexylbutanoyl)-1,3-thiazolidine-4-carboxamide	369.57	n/a	370.2	368.2
40		N-(5-aminopentyl)-3-([1,1'-biphenyl]-4-ylacetyl)-1,3-thiazolidine-4-carboxamide	411.57	90%	412.2	410.2

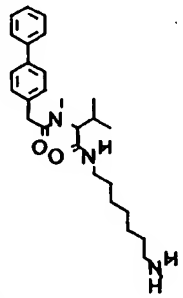
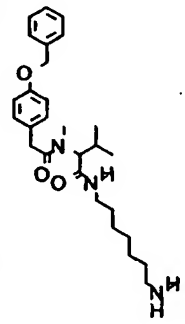
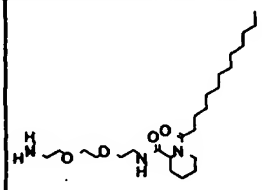
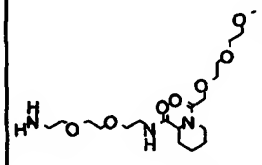
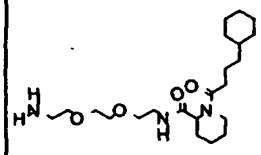
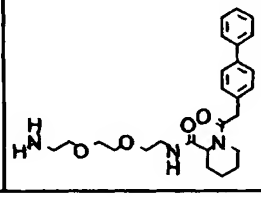
Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
41		N-(5-aminopentyl)-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide	441.60	93%	442.2	440.0
42		N-(5-aminopentyl)-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	457.71	96%	458.2	456.2
43		N-(5-aminopentyl)-2-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	421.54	97%	422.2	420.2
44		N-(5-aminopentyl)-2-(4-cyclohexylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	413.61	95%	414.2	412.2
45		N-(5-aminopentyl)-2-([1,1'-biphenyl]-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	455.61	94%	456.2	454.0
46		N-(5-aminopentyl)-2-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	485.63	94%	486.0	484.0
47		N-(1-{[(5-aminopentyl)amino]carbonyl}-2-methylpropyl)-N-methyltridecanamide	411.68	n/a	412.2	410.4
48		N-(5-aminopentyl)-11-methyl-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide	375.51	n/a	376.2	374.0

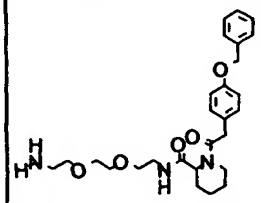
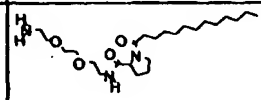
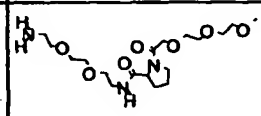
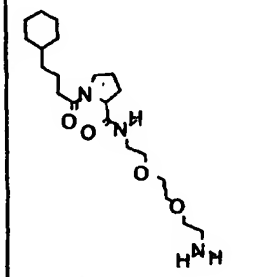
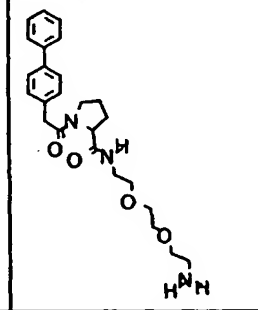
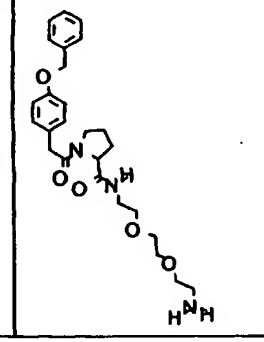
Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
49		N-(5-aminopentyl)-2-[(4-cyclohexylbutanoyl)(methyl)amino]-3-methylbutanamide	367.58	n/a	368.2	366.2
50		N-(5-aminopentyl)-2-[([1,1'-biphenyl]-4-ylacetyl)(methyl)amino]-3-methylbutanamide	409.58	86%	410.2	408.0
51		N-(5-aminopentyl)-3-methyl-2-[methyl({4-[(phenylmethyl)oxy]phenyl}acetyl) amino)butanamid	439.60	84%	440.2	438.0
52		N-(7-aminoheptyl)-1-tridecanoylpiperidine-2-carboxamide	437.72	n/a	438.4	436.4
53		N-(7-aminoheptyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl} piperidine-2-carboxamide	401.55	n/a	402.2	400.0
54		N-(7-aminoheptyl)-1-(4-cyclohexylbutanoyl)piperidine-2-carboxamide	393.62	n/a	394.2	392.2

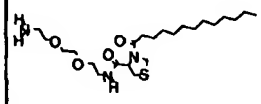
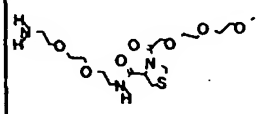
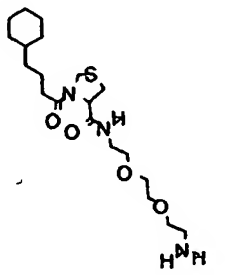
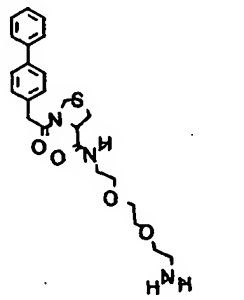
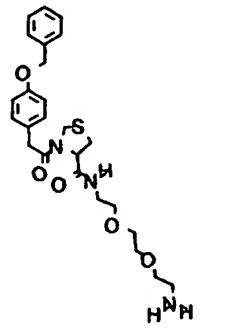
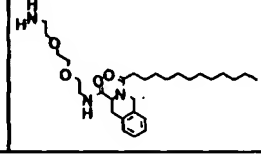
Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
55		N-(7-aminoheptyl)-1-([1,1'-biphenyl]-4-ylacetyl)piperidine-2-carboxamide	435.61	84%	436.2	434.0
56		N-(7-aminoheptyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)piperidine-2-carboxamide	465.64	85%	466.2	464.0
57		N-(7-aminoheptyl)-1-tridecanoylpyrrolidine-2-carboxamide	423.69	n/a	424.4	422.4
58		N-(7-aminoheptyl)-1-[[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl]pyrrolidine-2-carboxamide	387.52	n/a	388.2	386.0
59		N-(7-aminoheptyl)-1-(4-cyclohexylbutanoyl)pyrrolidine-2-carboxamide	379.59	n/a	380.2	378.0
60		N-(7-aminoheptyl)-1-([1,1'-biphenyl]-4-ylacetyl)pyrrolidine-2-carboxamide	421.59	97%	422.2	420.2

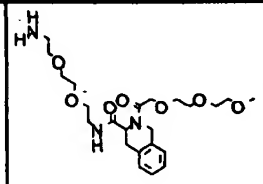
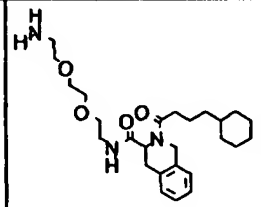
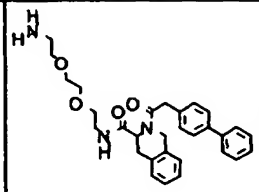
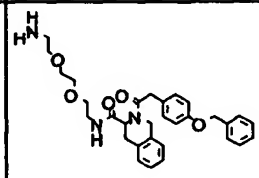
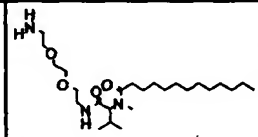
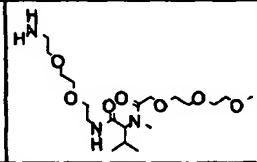
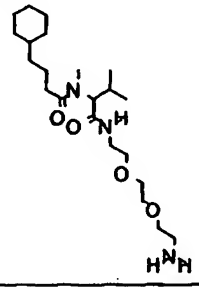
Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
61		N-(7-aminoheptyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carboxamide	451.61	95%	452.2	450.2
62		N-(7-aminoheptyl)-3-tridecanoyl-1,3-thiazolidine-4-carboxamide	441.73	n/a	442.4	440.2
63		N-(7-aminoheptyl)-3-[[(2-[[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl]-1,3-thiazolidine-4-carboxamide	405.56	n/a	406.2	404.2
64		N-(7-aminoheptyl)-3-(4-cyclohexylbutanoyl)-1,3-thiazolidine-4-carboxamide	397.63	n/a	398.2	396.0
65		N-(7-aminoheptyl)-3-([1,1'-biphenyl]-4-ylacetyl)-1,3-thiazolidine-4-carboxamide	439.62	89%	440.2	438.2
66		N-(7-aminoheptyl)-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide	469.65	93%	470.2	468.2

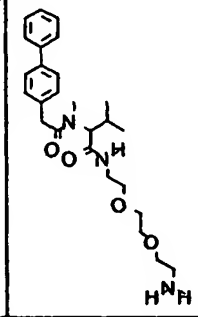
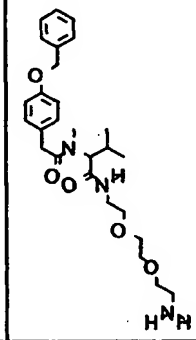
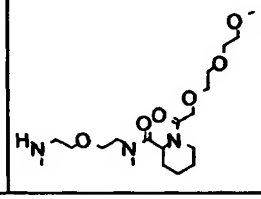
Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
67		N-(7-aminoheptyl)-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	485.76	97%	486.2	484.2
68		N-(7-aminoheptyl)-2-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	449.60	97%	450.2	448.2
69		N-(7-aminoheptyl)-2-(4-cyclohexylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	441.66	94%	442.2	440.4
70		N-(7-aminoheptyl)-2-([1,1'-biphenyl]-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	483.66	93%	484.2	482.0
71		N-(7-aminoheptyl)-2-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	513.69	93%	514.2	512.2
72		N-(1-{[(7-aminoheptyl)amino]carbonyl}-2-methylpropyl)-N-methyltridecanamide	439.73	n/a	440.4	438.4
73		N-(7-aminoheptyl)-11-methyl-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide	403.57	n/a	404.2	402.0
74		N-(7-aminoheptyl)-2-[(4-cyclohexylbutanoyl)(methyl)amino]-3-methylbutanamide	395.63	n/a	396.2	394.2

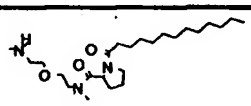
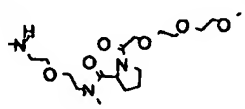
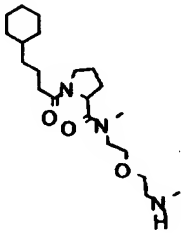
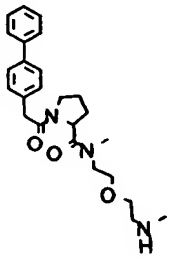
Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
75		N-(7-aminoheptyl)-2-[([1,1'-biphenyl]-4-ylacetyl)(methyl)amino]-3-methylbutanamide	437.63	88%	438.2	436.2
76		N-(7-aminoheptyl)-3-methyl-2-[methyl({4-[(phenylmethyl)oxy]phenyl}acetyl) amino]butanamide	467.66	78%	468.2	466.2
77		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-1-tridecanoylpiperidine-2-carboxamide	455.69	n/a	456.2	454.4
78		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-1-[[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl) piperidine-2-carboxamide	419.52	n/a	420.2	418.2
79		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-1-(4-cyclohexylbutanoyl)piperidine-2-carboxamide	411.59	n/a	412.2	410.2
80		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-1-([1,1'-biphenyl]-4-ylacetyl)piperidine-2-carboxamide	453.59	80%	454.2	452.2

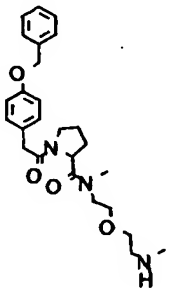
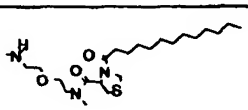
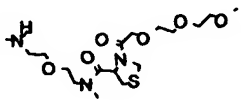
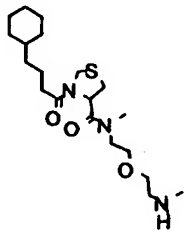
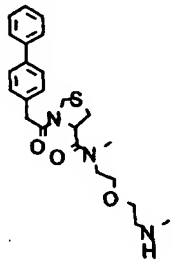
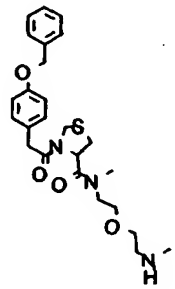
Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
81		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)piperidine-2-carboxamide	483.61	77%	484.2	482.2
82		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-1-tridecanoylpyrrolidine-2-carboxamide	441.66	n/a	442.2	440.2
83		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}pyrrolidine-2-carboxamide	405.50	n/a	406.2	404.0
84		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-1-(4-cyclohexylbutanoyl)pyrrolidine-2-carboxamide	397.56	n/a	398.2	396.2
85		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-1-([1,1'-biphenyl]-4-ylacetyl)pyrrolidine-2-carboxamide	439.56	95%	440.2	438.2
86		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carboxamide	469.59	96%	470.2	468.0

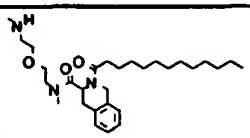
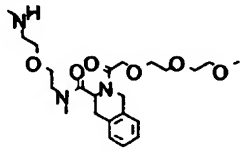
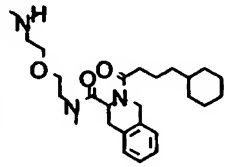
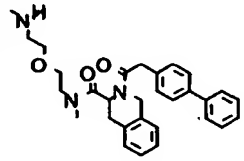
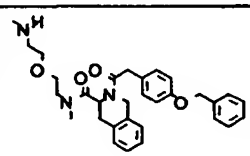
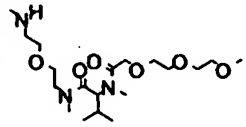
Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
87		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-3-tridecanoyl-1,3-thiazolidine-4-carboxamide	459.70	n/a	460.2	458.2
88		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide	423.53	n/a	424.2	422.2
89		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-3-(4-cyclohexylbutanoyl)-1,3-thiazolidine-4-carboxamide	415.60	n/a	416.0	414.2
90		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-3-([1,1'-biphenyl]-4-ylacetyl)-1,3-thiazolidine-4-carboxamide	457.60	91%	458.0	456.0
91		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide	487.62	92%	488.0	486.0
92		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	503.73	96%	504.2	502.2

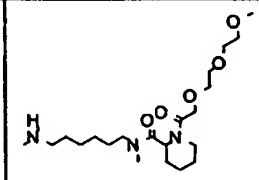
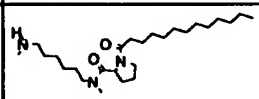
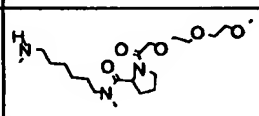
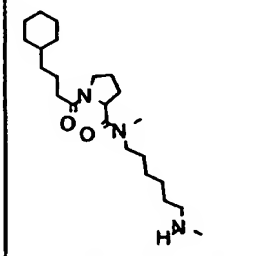
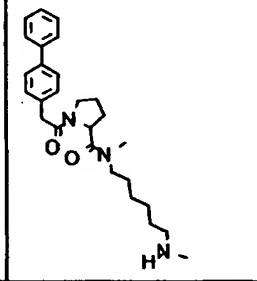
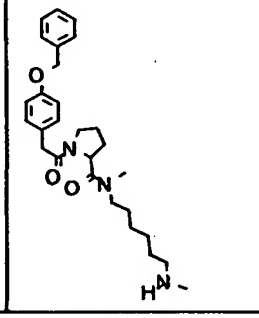
Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
93		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-2-[[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	467.57	95%	468.2	466.2
94		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-2-(4-cyclohexylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	459.63	81%	460.2	458.2
95		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-2-([1,1'-biphenyl]-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	501.63	92%	502.2	500.4
96		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-2-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	531.66	93%	532.2	530.2
97		N-[1-({[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]amino}carbonyl)-2-methylpropyl]-N-methyltridecanamide	457.70	n/a	458.2	456.2
98		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-11-methyl-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide	421.54	n/a	422.2	420.2
99		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-2-[(4-cyclohexylbutanoyl){methyl}amino]-3-methylbutanamide	413.61	n/a	414.2	412.2

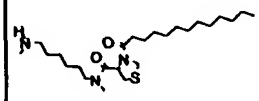
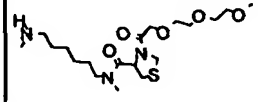
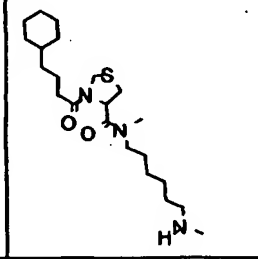
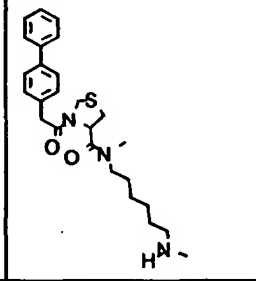
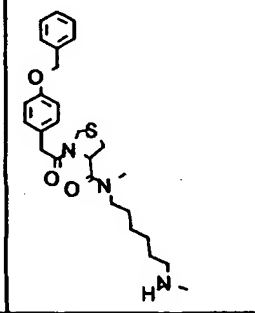
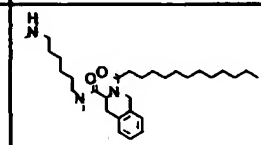
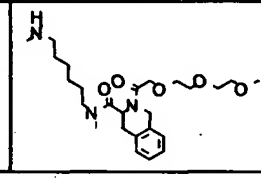
Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
100		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-2-[([1,1'-biphenyl]-4-ylacetyl)(methyl)amino]-3-methylbutanamide	455.60	78%	456.2	454.2
101		N-[2-({2-[(2-aminoethyl)oxy]ethyl}oxy)ethyl]-3-methyl-2-[methyl({4-[(phenylmethyl)oxy]phenyl}acetyl)amino]butanamide	485.63	61%	486.0	484.0
102		N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}piperidine-2-carboxamide	403.52	n/a	404.0	418.2

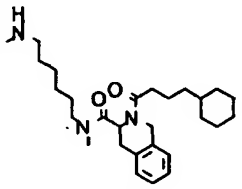
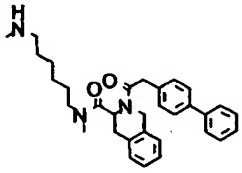
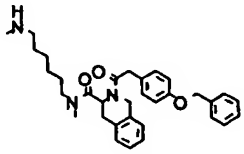
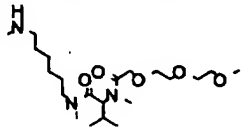
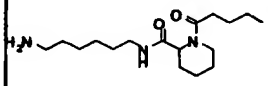
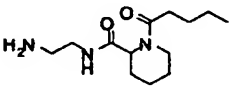
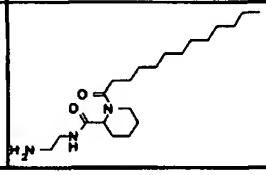
Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
103		N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1-tridecanoylpyrrolidine-2-carboxamide	425.66	n/a	426.2	-
104		N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}pyrrolidine-2-carboxamide	389.50	n/a	390.2	-
105		1-(4-cyclohexylbutanoyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)pyrrolidine-2-carboxamide	381.56	n/a	382.2	-
106		1-([1,1'-biphenyl]-4-ylacetyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)pyrrolidine-2-carboxamide	423.56	86%	424.2	-

Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
107		N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carboxamide	453.59	85%	454.0	-
108		N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-3-tridecanoyl-1,3-thiazolidine-4-carboxamide	443.70	n/a	444.4	-
109		N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide	407.53	n/a	408.0	-
110		3-(4-cyclohexylbutanoyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1,3-thiazolidine-4-carboxamide	399.60	n/a	400.2	-
111		3-([1,1'-biphenyl]-4-ylacetyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1,3-thiazolidine-4-carboxamide	441.60	93%	442.2	440.2
112		N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide	471.62	96%	472.2	470.2

Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
113		N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	487.73	91%	488.2	-
114		N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-2-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	451.57	97%	452.2	-
115		2-(4-cyclohexylbutanoyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	443.63	89%	444.4	-
116		2-([1,1'-biphenyl]-4-ylacetyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	485.63	93%	486.2	484.2
117		N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-2-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	515.66	94%	516.2	514.0
118		N,11-dimethyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide	405.54	n/a	406.2	-

Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
119		N-methyl-N-[6-(methylamino)hexyl]-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}ipiperidine-2-carboxamide	415.58	n/a	416.2	-
120		N-methyl-N-[6-(methylamino)hexyl]-1-tridecanoylpyrrolidine-2-carboxamide	437.72	n/a	438.4	-
121		N-methyl-N-[6-(methylamino)hexyl]-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}pyrrolidine-2-carboxamide	401.55	n/a	402.2	-
122		1-(4-cyclohexylbutanoyl)-N-methyl-N-[6-(methylamino)hexyl]pyrrolidine-2-carboxamide	393.62	n/a	394.2	-
123		1-([1,1'-biphenyl]-4-ylacetyl)-N-methyl-N-[6-(methylamino)hexyl]pyrrolidine-2-carboxamide	435.61	97%	436.2	-
124		N-methyl-N-[6-(methylamino)hexyl]-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carboxamide	465.64	95%	466.2	-

Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
125		N-methyl-N-[6-(methylamino)hexyl]-3-tridecanoyl-1,3-thiazolidine-4-carboxamide	455.75	n/a	456.2	-
126		N-methyl-N-[6-(methylamino)hexyl]-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide	419.59	n/a	420.2	-
127		3-(4-cyclohexylbutanoyl)-N-methyl-N-[6-(methylamino)hexyl]-1,3-thiazolidine-4-carboxamide	411.65	n/a	412.2	-
128		3-([1,1'-biphenyl]-4-ylacetyl)-N-methyl-N-[6-(methylamino)hexyl]-1,3-thiazolidine-4-carboxamide	453.65	90%	454.0	452.2
129		N-methyl-N-[6-(methylamino)hexyl]-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide	483.68	92%	484.2	482.0
130		N-methyl-N-[6-(methylamino)hexyl]-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	499.79	92%	500.4	-
131		N-methyl-N-[6-(methylamino)hexyl]-2-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	463.62	95%	464.2	-

Ex. No.	Structure	IUPAC Name	MW	purity% HPLC 220nM	FI-MS (APCI) m/z observed	
					pos.mode	neg.mode
132		2-(4-cyclohexylbutanoyl)-N-methyl-N-[6-(methylamino)hexyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	455.69	91%	456.2	-
133		2-([1,1'-biphenyl]-4-ylacetyl)-N-methyl-N-[6-(methylamino)hexyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	497.69	91%	498.4	496.0
134		N-methyl-N-[6-(methylamino)hexyl]-2-((4-[(phenylmethyl)oxy]phenyl)acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide	527.71	92%	528.4	526.4
135		N,11-dimethyl-N-[6-(methylamino)hexyl]-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide	417.59	n/a	418.2	-
136		N-(6-aminohexyl)-1-pentanoylpiperidine-2-carboxamide	311.47	100%	310.2	312.2
137		N-(2-aminoethyl)-1-pentanoylpiperidine-2-carboxamide	255.36	90%	254.2	256.2
138		N-(2-aminoethyl)-1-tridecanoylpiperidine-2-carboxamide	367.58	93%	368.0	366.2

Example 139 : Preparation of a pharmaceutical formulation

[0107] The following formulation examples illustrate representative pharmaceutical compositions of this invention containing compounds according to formula I. The present invention, however, is not limited to the following pharmaceutical compositions.

Formulation 1 — Tablets

[0108] A compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ration. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 240-270 mg tablets

(80-90 mg of active amino derivatives according to formula I per tablet) in a tablet press.

Formulation 2 — Capsules

[0109] A compound of formula I is admixed as a dry powder with a starch diluent in an approximate 1:1 weight ratio. The mixture is filled into 250 mg capsules (125 mg of active amino derivatives according to formula I per capsule).

Formulation 3 — Liquid

[0110] A compound of formula I (1250 mg), sucrose (1.75 g) and xanthan gum (4 mg) are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of microcrystalline cellulose and sodium carboxymethyl cellulose (11:89, 50 mg) in water. Sodium benzoate (10 mg), flavor, and color are diluted with water and added with stirring. Sufficient water is then added to produce a total volume of 5 mL.

Formulation 4 — Tablets

[0111] The compound of formula I is admixed as a dry powder with a dry gelatin binder in an approximate 1:2 weight ratio. A minor amount of magnesium stearate is added as a lubricant. The mixture is formed into 450-900 mg tablets (150-300 mg of active amino derivatives according to formula I) in a tablet press.

Formulation 5 — Injection

[0112] The compound of formula I is dissolved in a buffered sterile saline injectable aqueous medium to a concentration of approximately 5 mg/ml.

[0113] In the following the present invention shall be illustrated by means of some examples which are not construed to be viewed as limiting the scope of the invention.

Example 46 : Biological assays

a) Production of Recombinant Bax

[0114] Human Bax-α lacking 20 amino acids at the COOH-terminus is expressed as a GST fusion protein or a His-tagged protein in *Escherichia coli,* and the protein is purified from the soluble cell fraction. In brief, the GST-Bax fusion protein is applied to a glutathione-Sepharose column, and Bax was released by cleavage with thrombin (0.6U/mL). Bax is subsequently purified on heparin-Sepharose, followed by fast protein liquid chromatography (FPLC) Mono Q. His-tagged Bax is purified on a Ni-nitriloacetic acid-agarose column followed by FPLC MonoQ:

b) Isolation of Mitochondria

[0115] Mitochondria are isolated from mouse liver cells by differential centrifugation. Cells are broken with a dounce homogenizer and the suspension is centrifuged at 2,000 g in an Eppendorf centrifuge at 4 °C. This procedure is repeated until almost all the cells are broken. Supernatants from each step are pooled before centrifugation at 13,000 g at 4 °C for 10 min. The pellet is resuspended in 40 mL MB buffer and centrifuged at 2000 g for 2 min. The supernatant is removed and centrifuged at 13 kg for 4 min. The mitochondria are recovered in the 13k pellet and resuspended in MB buffer at a density of 30 OD600 nm/mL.

c) In Vitro Assay for Cytochrome c Release

[0116] Mitochondria (30 µg) from mouse liver are incubated with 200 nM recombinant Bax in the presence of various compounds (5 µM) in 200 µL of KCl buffer for 20 min at 30 °C and are then centrifuged for 4 min at 13,000 g at 4 °C. Mitochondrial pellets corresponding to 1.5 µg proteins are separated by SDS-PAGE using 4-20% Tris-Gly gels (NOVEX) and their respective contents of cytochrome c are estimated by Western blotting using polyclonal anti-cytochrome c antibody (dilution 1:2,500). Antigen-antibody complexes are detected using horseradish peroxidase-conjugated goat anti-rabbit IgG and enhance chemiluminescence detection reagents. The cytochrome c bands are scanned and quantified using a Bio-Rad (GS-700 Imaging Densitometer).

d) Effect of Compounds according to formula I onto the Release of Cytochrome c Triggered by Bid-Induced Bax Activation (in vitro assay)

[0117] Concerning the Bid-induced activation of Bax leading to mitochondrial Cytochrome C release, it is referred to the description of Martinou et al. in *The Journal of Cell Biology,* Vol. 144, No. 5, March 8, 1999, pages 891-901 as well as Eskes, Desagher, Antonsson and Martinou in *Molecular and Cellular Biology,* February 2000, p. 929-935, Vol. 20, No. 3. Mitochondria isolated from HeLa cells are incubated for 15 min at 30°C in 100 µl of KCl buffer in the presence or absence of 10 nM recombinant Bid. The various compounds (10 µM) are pre-incubated for 5 min prior to addition of Bid. Following incubation, mitochondria were centrifuged for 5 min at 13000 g at 4°C and the supernatant is collected for cytochrome c analysis. Cytochrome c is detected by Western blotting. The cytochrome c bands are scanned and quantified using a Bio-Rad (GS-700 Imaging Densitometer).

[0118] The above set out 2 *in vitro* assays c) and d) involving the determination of mitochondrial cytochrome c release are based on immunochemical methods using the Western blot analysis. Alternatively, said quantitative cytochrome c determinations could be performed by using spectrophotometric means :

I. by recording the difference between reduced and oxidised cytochrome c by dual wavelength double beam spectrophotometry;

II. by measuring the rather intensive γ or Soret peak in the spectrum of cytochrome c ($\varepsilon = 100\ mM^{-1}cm^{-1}$) is used for rapid and quantitative determination of the release of cytochrome c from isolated mitochondria. This technique allows a highly convenient, fast and reliable quantitative determination of the release of cytochrome c.

e) Sympathetic Neuron Culture and Survival Assay (in vitro assay)

[0119] Sympathetic neurons from superior cervical ganglia (SCG) of newborn rats (p4) are dissociated in dispase, plated at a density of 104 cells/cm^2 in 48 well MTT plates coated with rat tail collagen, and cultured in Leibowitz medium containing 5% rat serum, 0.75 g/ml NGF 7S (Boehringer Mannheim Corp., Indianapolis, IN.) and arabinosine 105M. Cell death is induced at day 4 after plating by exposing the culture to medium containing 10 g/ml of anti NGF antibody (Boehringer Mannheim Corp., Indianapolis, IN.) and no NGF or arabinosine, in the presence or absence of amino derivatives according to formula I. 24 hours after cell death induction, determination of cell viability is performed by incubation of the culture for 1 hour, at 37°C in 0.5 mg/ml of 3-(4,5-dimethyl-thiazol-2-yl)2,5 diphenyl tetrazolium bromide (MTT). After incubation in MTT cells are re-suspended in DMSO, transferred to a 96 MTT plate and cell viability is evaluated by meas-uring optical density at 590 nm.

f) Biological Results

[0120] To illustrate the present invention, the biological activity of a few compounds described as examples above is summarized in the following table.

Compound	Mitochondria Cytochrome c Release Triggered by Bid-Induced Bax Activation (% Inhibition) [a]	Mitochondria Cytochrome c Release Triggered by Bax Activation (% Inhibition) [b]	Neuronal Survival [a] (%)
1	-	47	33
2	17	-	41
7	88	-	-
22	-	95	22

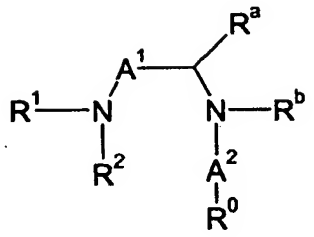
a) Compounds were tested at 10 µM

b) Compounds were tested at 5 µM

[0121] The above indicated values refer to the inhibition (in %) of the mitochondrial cyctochrome c release upon using the corresponding test compounds 1, 2, 7 and 22 given in an exemplary way. From the above table, it could be derived that the test compounds according to the formula I do have a significant effect both on the inhibition of release of cytochrome c and on the neuronal survival. It notably turns out that a neuronal survival rate could be achieved with the compounds according to formula I, as they both inhibit Bax directly as well as indirectly.

Claims

1. Amine derivatives according to formula I:



I

and its geometrical isomers, in an optically active form as enantiomers, diastereomers, as well as in the form of racemate, as well as pharmaceutically acceptable salts thereof, wherein

A^1 and A^2 are selected independently from each other from the group consisting of-C(O)- and -SO_2-;

R^a is C_1-C_{10} alkyl, R^b is CH_3, or

R^a and R^b taken together with the atoms to which they are attached form a five-membered saturated ring optionally containing a sulfur atom or a six-membered saturated ring optionally fused with an aryl or heteroaryl group;

R^1 is either H or C_1-C_6 alkyl;

R^2 is -$(R^d$-$X_1)_m$-R^e wherein m is an integer from 0 to 8; whereby

R^d is selected of aryl, heteroaryl, C_1-C_{18} alkyl, 3-8-membered cycloalkyl, C_2-C_{18} alkenyl or 3-8-membered cycloalkenyl, C_2-C_{18} alkynyl;

X_1 is a bond, O, NH, NR^g, $NR^gN^{g'}$, S, $Si(R^gR^{g'})$, SO, SO_2, wherein R^g and $R^{g'}$ are independently selected from the group consisting of substituted or unsubstituted C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl or heteroaryl;

R^e is selected of aryl- C_1-C_{18} alkyl, aryl- C_2-C_{18} alkenyl, aryl- C_2-C_{18} alkynyl, heteroaryl- C_1-C_{18} alkyl, heteroaryl- C_2-C_{18} alkenyl, heteroaryl- C_2-C_{18} alkynyl, C_1-C_{18} alkyl, C_2-C_{18} alkenyl, C_2-C_{18} alkynyl, said C_1-C_{18} alkyl, C_2-C_{18} alkenyl and C_2-C_{18} alkynyl have a polar terminal substituent of the formula -NRR' or —N^+RR'R" wherein R, R', R" are H, C_1-C_6-alkyl; or

R^1 and R^2 together with the N atom to which they are attached form an unsubstituted or substituted 4-12 membered unsaturated or saturated ring containing one further heteroatom selected from O, N being optionally substituted by R^e, or

R^1 and R^2 together with the N atom to which they are attached form an unsubstituted or substituted 4-12 membered unsaturated or saturated ring being substituted by R^e, or by a polar terminal substituent of the formula -NRR' or —N^+RR'R" wherein R, R', R" are H, C_1-C_6-alkyl;

R^0 is R^f-X_2-$R^{f'}$ wherein

R^f and $R^{f'}$ are independently from each other selected from the group consisting of aryl, heteroaryl, 3-8-membered cycloalkenyl, 3-8-membered cycloalkyl, C_2-C_{18} alkyl, C_2-C_{18} alkenyl, C_2-C_{18} alkynyl, aryl- C_1-C_{18} alkyl, aryl- C_2-C_{18} alkenyl, aryl-C_2-C_{18} alkynyl, heteroaryl- C_1-C_{18} alkyl, heteroaryl- C_2-C_{18} alkenyl, heteroaryl- C_2-C_{18} alkynyl;

X_2 is a bond or O, S, Si($R^9R^{9'}$), SO, SO_2, wherein R^9 and $R^{9'}$ are selected as above defined.

2. An amine derivative according to claim 1, wherein A^1 and A^2 are each C=O.

3. An amine derivative according to claim 1 or 2, wherein R^0 is C_8-C_{18} alkyl, more preferred C_{10}-C_{18} alkyl and most preferred C_{12} alkyl.

4. An amine derivative according to any of the preceding claims wherein R^e is C_{10}-C_{18} alkyl having a terminal NH_2 or ammonium group.

5. An amine derivative according to any of the preceding claims wherein R^a and R^b form a five-membered saturated ring optionally containing a sulfur atom, or a six-membered saturated ring wherein said ring may be fused with an unsubstituted phenyl group.

6. An amine derivative according to claim 5 wherein said ring is pyrrolidinyl, piperidinyl, tetrahydroisoquinolinyl (TIC) or 1,3-thiazolidinyl.

7. An amine derivative according to any of the preceding claims wherein R^1 is H or CH_3, R^2 is -$(R^d$-$X_1)_m$-R^e in which R^d-X_1 is -$(CH_2)_2$-O- or a bond, R^e is C_1-C_{10}-alkylamine, m is 1, 2 or 3.

8. An amine derivative according to claim 7, wherein R^2 is a C_2-C_8 alkylamine.

9. An amine derivative according to claim 8, wherein R^2 is ethylenamine, hexylenamin or heptylenamine.

10. An amine derivative according to any of the preceding claims, wherein R^0 is selected from the group consisting of unsubstituted C_4-C_{16} alkyl, a C_4-C_{16} alkyl having a terminal cyclohexyl group, more preferred C_6-C_{14} alkyl, -CH_2-phenyl-O-CH_2-phenyl or -CH_2-Ph-Ph.

11. An amine derivative according to claim 10, wherein R^0 is dodecacyl.

12. An amine derivative according to any of the preceding claims wherein R^a and R^b form a five-membered saturated ring which may contain a sulfur atom or a six-membered saturated ring optionally fused with an unsubstituted phenyl group, A^1 and A^2 are each C=O, R^0 is an unsubstituted C_4-C_{16} alkyl having optionally a terminal cyclohexyl group or -CH_2-Ph-O-CH_2-Ph or CH_2-Ph-Ph, R^1 is H or -CH_3, R^2 is -$(R^d$-$X_1)_m$-R^e wherein R^d-X_1 is -$(CH_2)_2$-O- with m being 0 or 2, R^e is an unsubstituted C_2-C_8-alkylamine.

13. An amine derivative according to claim 12, wherein R^e is C_2-C_7 alkylamine and most preferred hexylamine.

14. An amine derivative according to any of the preceding claims wherein R^a and R^b form a piperidinyl, pyrrolidinyl or thiazolidinyl ring optionally fused with an unsubstituted phenyl group, A^1 and A^2 are each C=O, R^0 is an unsubstituted C_4 or C_{12} alkyl chain, R^1 is H or CH_3, R^2 is -$(R^d$-$X_1)_m$-R^e wherein m is 0 and R^e is C_2-C_8 alkylamine.

15. An amine derivative according to any of the preceding claims wherein R^b is CH_3, R^a is iPr, A^1 and A^2 are each C=O, R^0 is C_4-C_{15} alkyl, preferably a dodecacyl group, R^1 is H, R^2 is -$(R^d$-$X_1)_m$-R^e wherein m is 0, R^e is C_4-C_{10}, particularly C_6 alkylamine.

16. An amine derivative according to any of the preceding claims selected from the following group:

(S)-N-(6-Aminohexyl)-1-tridecanoylpiperidine-2-carboxamide

(R)-N-(6-Aminohexyl)-1-tridecanoylpiperidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}piperidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-(4-cyclohexylbutanoyl)piperidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-([1,1'-biphenyl]-4-ylacetyl)piperidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)piperidine-2-carboxamide

(S)-N-(6-Aminohexyl)-1-tridecanoylpyrrolidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}pyrrolidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-(4-cyclohexylbutanoyl)pyrrolidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-([1,1'-biphenyl]-4-ylacetyl)pyrrolidine-2-carboxamide

(±)-N-(6-Aminohexyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carbox-amide

(±)-N-(6-Aminohexyl)-3-tridecanoyl-1,3-thiazolidine-4-carboxamide

(±)-N-(6-Aminohexyl)-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide

(±)-N-(6-Aminohexyl)-3 -(4-cyclohexylbutanoyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(6-Aminohexyl)-3-([1,1'-biphenyl]-4-ylacetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(6-Aminohexyl)-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(6-Aminohexyl)-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(6-Aminohexyl)-2-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(6-Aminohexyl)-2-(4-cyclohexylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(6-Aminohexyl)-2-([1,1'-biphenyl]-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(6-Aminohexyl)-2-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,2,3,4 tetrahydroisoquinoline-3 -carboxamide

(S)-N-(1-{[(6-Aminohexyl)amino]carbonyl}-2-methylpropyl)-N-methyltridecanamide

(±)-N-(6-Aminohexyl)-11-methyl-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide

(±)-N-(6-Aminohexyl)-2-[(4-cyclohexylbutanoyl)(methyl)amino]-3-methylbutanamide

(±)-N-(6-Aminohexyl)-2-[([1,1'-biphenyl]-4-ylacetyl)(methyl)amino]-3-methylbutanamide

(±)-N-(6-Aminohexyl)-3-methyl-2-[methyl({4-[(phenylmethyl)oxy]phenyl}acetyl)amino]butanamide

(±)-N-(5-Aminopentyl)-1-tridecanoylpiperidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}piperidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-(4-cyclohexylbutanoyl)piperidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-([1,1'-biphenyl]-4-ylacetyl)piperidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-({4-[(phenylmethyl)oxy]phenyl} acetyl)piperidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-tridecanoylpyrrolidine-2-carboxamide

(±)-N-(5 -Aminopentyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}pyrrolidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-(4-cyclohexylbutanoyl)pyrrolidine-2-carboxamide

(±)-N-(5-Aminopentyl)-1-([1,1'-biphenyl]-4-ylacetyl)pyrrolidine-2-carboxamide

(±)-N-(5 -Aminopentyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carbox-amide

(±)-N-(5-Aminopentyl)-3-tridecanoyl-1,3-thiazolidine-4-carboxamide

(±)-N-(5-Aminopentyl)-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide

(±)-N-(5-Aminopentyl)-3 -(4-cyclohexylbutanoyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(5-Aminopentyl)-3-([1,1'-biphenyl]-4-ylacetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(5-Aminopentyl)-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(5-Aminopentyl)-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(5-Aminopentyl)-2-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-((5-Aminopentyl)-2-(4-cyclohexylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(5-Aminopentyl)-2-([1,1'-biphenyl]-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline-3 -carboxamide

(±)-N-(5-Aminopentyl)-2-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,2,3,4-tetrahydroisoquinoline-3 -carboxamide

(±)-N-(1-{[(5-Aminopentyl)amino]carbonyl}-2-methylpropyl)-N-methyltridecanamide

(±)-N-(5-Aminopentyl)-11-methyl-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide

(±)-N-(5-Aminopentyl)-2- [(4-cyclohexylbutanoyl)(methyl)amino]-3-methylbutanamide

(±)-N-(5-Aminopentyl)-2-[([1,1'-biphenyl]-4-ylacetyl)(methyl)amino]-3-methylbutanamide

(±)-N-(5-Aminopentyl)-3-methyl-2-[methyl({4-[(phenylmethyl)oxy]phenyl}acetyl)amino]butanamide

(±)-N-(7-Aminoheptyl)-1-tridecanoylpiperidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}piperidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-(4-cyclohexylbutanoyl)piperidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-([1,1'-biphenyl]-4-ylacetyl)piperidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)piperidine-2-carboxamide

(+)-N-(7-Aminoheptyl)-1-tridecanoylpyrrolidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}pyrrolidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-(4-cyclohexylbutanoyl)pyrrolidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-([1,1'-biphenyl]-4-ylacetyl)pyrrolidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carboxamide

(±)-N-(7-Aminoheptyl)-3-tridecanoyl-1,3-thiazolidine-4-carboxamide

(±)-N-(7-Aminoheptyl)-3-{[(2-{ [2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide

(±)-N-(7-Aminoheptyl)-3-(4-cyclohexylbutanoyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(7-Aminoheptyl)-3-([1,1'-biphenyl]-4-ylacetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(7-Aminoheptyl)-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-(7-Aminoheptyl)-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(7-Aminoheptyl)-2-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(7-Aminoheptyl)-2-(4-cyclohexylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(7-Aminoheptyl)-2-([1,1'-biphenyl]-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(7-Aminoheptyl)-2-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-(1-{[(7-Aminoheptyl)amino]carbonyl}-2-methylpropyl)-N-methyltridecanamide

(±)-N-(7-Aminoheptyl)-11-methyl-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide

(±)-N-(7-Aminoheptyl)-2-[(4-cyclohexylbutanoyl)(methyl)amino]-3-methylbutanamide

(±)-N-(7-Aminoheptyl)-2-[([1,1'-biphenyl]-4-ylacetyl)(methyl)amino]-3-methylbutanamide

(±)-N-(7-Aminoheptyl)-3-methyl-2-[methyl({4-[(phenylmethyl)oxy]phenyl}acetyl)amino]butanamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-tridecanoylpiperidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}piperidine-2-carboxamide

(+)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-(4-cyclohexylbutanoyl)piperidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-([1,1'-biphenyl]-4-ylacetyl)piperidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)piperidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-tridecanoylpyrrolidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-{[(2-{[2-(methyloxy)ethyl]oxy} ethyl)oxy] acetyl} pyrrolidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-(4-cyclohexylbutanoyl)pyrrolidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-([1,1'-biphenyl]-4-ylacetyl)pyrrolidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-1-({4-[(phenylmethyl)oxy]phenyl } acetyl)pyrrolidine-2-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-3-tridecanoyl-1,3-thiazolidine-4-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-3-{[(2-{[2-(methyloxy)ethyl]oxy}-ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-3-(4-cyclohexylbutanoyl)-1,3-thiazolidine-4-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-3-([1,1'-biphenyl]-4-ylacetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-2-{[(2-{[2-(methyloxy)ethyl]oxy}-ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl] -2-(4-cyclohexylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-2-([1,1'-biphenyl]-4-ylacetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-2-({4-[(phenylmethyl)oxy]phenyl} acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-[1-({[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]amino}carbonyl)-2-methylpropyl]-N-methyltridecanamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-11-methyl-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-2-[(4-cyclohexylbutanoyl)(methyl)-amino]-3-methylbutanamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-2-[([1,1'-biphenyl]-4-ylacetyl)(methyl)-amino]-3-methylbutanamide

(±)-N-[2-({2-[(2-Aminoethyl)oxy]ethyl}oxy)ethyl]-3-methyl-2-[methyl({4-[(phenylmethyl)oxy]phenyl}acetyl)amino]butanamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy} ethyl)-1-{[(2-{[2-(methyloxy)ethyl]-oxy}ethyl)oxy] acetyl}piperidine-2-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1-tridecanoylpyrrolidine-2-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}pyrrolidine-2-carboxamide

(±)-1-(4-Cyclohexylbutanoyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy} ethyl)pyrrolidine-2-carboxamide

(±)-1-([1,1'-Biphenyl]-4-ylacetyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-pyrrolidine-2-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1-({4-[(phenylmethyl)oxy]phenyl} acetyl)pyrrolidine-2-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-3-tridecanoyl-1,3-thiazolidine-4-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide

(±)-3-(4-Cyclohexylbutanoyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1,3-thiazolidine-4-carboxamide

(±)-3-([1,1'-Biphenyl]-4-ylacetyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1,3-thiazolidine-4-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-2-tridecanoyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-2-{[(2-{[2-(methyloxy)ethyl]oxy}-ethyl)oxy]acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-2-(4-Cyclohexylbutanoyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-2-([1,1'-Biphenyl]-4-ylacetyl)-N-methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-Methyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-2-({4-[(phenylmethyl)oxy]phenyl} acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N,11-Dimethyl-N-(2-{[2-(methylamino)ethyl]oxy}ethyl)-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}piperidine-2-carboxamide

(±)-N-Methyl-N- [6-(methylamino)hexyl]-1-tridecanoylpyrrolidine-2-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-1-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}pyrrolidine-2-carboxamide

(±)-1-(4-Cyclohexylbutanoyl)-N-methyl-N-[6-(methylamino)hexyl]pyrrolidine-2-carboxamide

(±)-1-([1,1'-Biphenyl]-4-ylacetyl)-N-methyl-N-[6-(methylamino)hexyl]pyrrolidine-2-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-1-({4-[(phenylmethyl)oxy]phenyl}acetyl)pyrrolidine-2-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-3-tridecanoyl-1,3-thiazolidine-4-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-3-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]acetyl}-1,3-thiazolidine-4-carboxamide

(±)-3-(4-Cyclohexylbutanoyl)-N-methyl-N-[6-(methylamino)hexyl]-1,3-thiazolidine-4-carboxamide

(±)-3-([1,1'-Biphenyl]-4-ylacetyl)-N-methyl-N-[6-(methylamino)hexyl]-1,3-thiazolidine-4-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-3-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,3-thiazolidine-4-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-2-tridecanoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N-Methyl-N-[6-(methylamino)hexyl]-2-{[(2-{[2-(methyloxy)ethyl]oxy}ethyl)oxy]-acetyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-2-(4-Cyclohexylbutanoyl)-N-methyl-N-[6-(methylamino)hexyl]-1,2,3,4-tetrahydro-isoquinoline-3-carboxamide

(±)-2-([1,1'-Biphenyl]-4-ylacetyl)-N-methyl-N-[6-(methylamino)hexyl]-1,2,3,4-tetra-hydroisoquinoline-3-carboxamide

(+)-N-Methyl-N-[6-(methylamino)hexyl]-2-({4-[(phenylmethyl)oxy]phenyl}acetyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

(±)-N,11-Dimethyl-N-[6-(methylamino)hexyl]-12-(1-methylethyl)-10-oxo-2,5,8-trioxa-11-azatridecan-13-amide

(±)-N-(6-Aminohexyl)-1-pentanoylpiperidine-2-carboxamide

(±)-N-(2-Aminoethyl)-1-pentanoylpiperidine-2-carboxamide

17. An amine derivative according to claim 16, which is selected from the group consisting of:

(S)-N-(6-Aminohexyl)-1-tridecanoylpiperidine-2-carboxamide

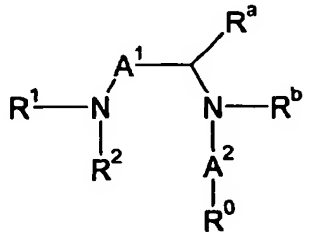
(R)-N-(6-Aminohexyl)-1-tridecanoylpiperidine-2-carboxamide

(S)-N-(6-Aminohexyl)-1-tridecanoylpyrrolidine-2-carboxamide

(S)-N-(1-{[(6-Aminohexyl)amino]carbonyl}-2-methylpropyl)-N-methyltridecanamide

18. An amine derivative according to any of the preceding claims for use as a medicament.

19. Use of an amine derivative according to formula I:



I

with its geometrical isomers, in an optically active form as enantiomers, diastereomers, as well as in the form of racemate, as well as pharmaceutically acceptable salts thereof, wherein

A^1 and A^2 are selected independently from each other from the group consisting of- -(C=O)- and $-SO_2-$;

R^a is C_1-C_{10} alkyl, R^b is CH_3, or

R^a and R^b taken together with the atoms to which they are attached form a five-membered saturated ring optionally containing a sulfur atom or a six-membered saturated ring optionally fused with an aryl or heteroaryl group;

R^1 is either H or C_1-C_6 alkyl;

R^2 is $-(R^d-X_1)_m-R^e$ wherein m is an integer from 0 to 8 and whereby

R^d is selected of aryl, heteroaryl, C_1-C_{18} alkyl, 3-8-membered cycloalkyl, C_2-C_{18} alkenyl or 3-8-membered cycloalkenyl, C_2-C_{18} alkynyl;

X_1 is a bond, O, NH, NR^9, $NR^9N^{9'}$, S, $Si(R^9R^{9'})$, SO, SO_2, wherein R^9 and $R^{9'}$ are independently selected from the group consisting of substituted or unsubstituted C_1-C_6 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, aryl or heteroaryl;

R^e is selected of aryl- C_1-C_{18} alkyl, aryl- C_2-C_{18} alkenyl, aryl- C_2-C_{18} alkynyl, heteroaryl- C_1-C_{18} alkyl, heteroaryl- C_2-C_{18} alkenyl, heteroaryl- C_2-C_{18} alkynyl, C_1-C_{18} alkyl, C_2-C_{18} alkenyl, C_2-C_{18} alkynyl, said C_1-C_{18} alkyl, C_2-C_{18} alkenyl and C_2-C_{18} alkynyl have a polar terminal substituent of the formula OR, -NRR' or-N^+RR'R" wherein R, R', R" are H, C_1-C_6-alkyl; or

R^1 and R^2 together with the N atom to which they are attached form an unsubstituted or substituted 4-12 membered unsaturated or saturated ring containing one further heteroatom selected from O, N being optionally substituted by R^e, or

R^1 and R^2 together with the N atom to which they are attached form an unsubstituted or substituted 4-12 membered unsaturated or saturated ring being substituted by R^e, or by a polar terminal substituent of the formula OR, -NRR' or —N^+RR'R" wherein R, R', R" are H, C_1-C_6-alkyl;

R^0 is R^f-X_2-$R^{f'}$ wherein

R^f and $R^{f'}$ are independently from each other selected from the group consisting of aryl, heteroaryl, 3-8-membered cycloalkenyl, 3-8-membered cycloalkyl, C_2-C_{18} alkyl, C_2-C_{18} alkenyl, C_2-C_{18} alkynyl, aryl- C_1-C_{18} alkyl, aryl- C_2-C_{18} alkenyl, aryl-C_2-C_{18} alkynyl, heteroaryl- C_1-C_{18} alkyl, heteroaryl- C_2-C_{18} alkenyl, heteroaryl- C_2-C_{18} alkynyl;

X_2 is a bond or O, S, $Si(R^9R^{9'})$, SO, SO_2, wherein R^9 and $R^{9'}$ are selected as above defined, for the preparation of a pharmaceutical composition for the treatment of disorders associated with the modulation of the Bax function and/or the Bax activation.

20. Use according to claim 19, wherein the terminal substituent of R^e is -NH_2 or an ammonium moiety.

21. Use according to claim 19 or 20 for the treatment or prevention of disorders associated with the abnormal expression or activity of Bax by inhibition of the Bax function or the Bax activation.

22. Use according to any of claims 19 to 21 for the treatment of neuronal disorders including Alzheimer's disease, Parkinson's disease, diseases associated with polyglutamine tracts including Huntington's disease, spinocerebellar ataxias and dentatorubral-pallidolysian atrophy, amyotrophic lateral sclerosis, Crohn's disease, retinis pigmentosa and multiple sclerosis and epilepsy.

23. Use according to any of claims 19 to 21 for the treatment of ischemia including stroke, myocardial infarction and reperfusion injury, cardiovascular disorders, arteriosclerosis, heart failure, heart transplantation.

24. Use according to any of claims 19 to 21 for the treatment of renal hypoxia, hepatitis, AIDS.

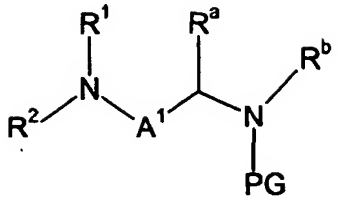
25. Use according to any of claims 19 to 21 for the treatment of infertility related disorders including premature menopause, ovarian failure and follicular atresia.

26. Use of an amine derivative according to any of claims 1 to 17 for the preparation of a pharmaceutical composition for oral administration.

27. A pharmaceutical composition containing at least one amino derivatives according to any of the claims 1 to 17 and a pharmaceutically acceptable carrier, diluent or excipient thereof.

28. Process for the preparation of amine derivatives according to any of the claims 1 to 17, whereby

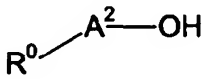
a) a compound according to the following general formula



IV

whereby PG is a protective group and the substituents R^1, R^2, A^1, R^a and R^b are as above defined and

b) is reacted, after a deprotection step, with an electrophile derivative according to the general formula



V

whereby A^2 and R^0 are as above defined.

29. Process according to claim 28, wherein A^1 and A^2 are each -C=O and R^1, R^2, R^a and R^b are as above defined.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 00 81 0128

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
A	WO 97 31898 A (ARIAD GENE THERAPEUTICS INC ;HOLT DENNIS A (US); KEENAN TERENCE P) 4 September 1997 (1997-09-04) * page 103, line 26; claim 1 *	1-29	C07D211/60 A61K31/445 C07D207/16 A61K31/40 A61P43/00
A	WO 92 19593 A (VERTEX PHARMA) 12 November 1992 (1992-11-12) * claim 1 *	1	C07D277/06 A61K31/425 A61K31/47 C07D217/26
A	WO 92 00278 A (VERTEX PHARMA) 9 January 1992 (1992-01-09) * claim 1 *	1	C07C233/60 C07C235/00
A	WO 95 12581 A (EXSYMOL SA ;BABIZHAYEV MARC (RU); SEGUIN MARIE CHRISTINE (FR)) 11 May 1995 (1995-05-11) * claim 1 *	1	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

C07D
A61K

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
MUNICH	4 July 2000	Gettins, M

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 00 81 0128

Claim(s) searched incompletely:
1-29

Reason for the limitation of the search:

Present claims 1-29 relate to an extremely large number of possible compounds. Support within the meaning of Article 84 EPC and/or disclosure within the meaning of Article 83 EPC is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds in Formula I, where A1 and A2 = C(O), R1 = H , Ra and Rb together form a ring, Re is -NH2.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 81 0128

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04-07-2000

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